09/446601

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 7,323,493 Attorney Docket No. IVD000994 US PCT

Application No. 09/446,601 Issue Date: January 29, 2008

Patentees: Bernard Abramovici, Jean-Claude Gautier, Jean-Claude Gromenil, and Jean-Marie Marrier

Title: SOLID PHARMACEUTICAL COMPOSITION CONTAINING BENZOFURAN DERIVATIVES

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United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. §156

Pursuant to 35 U.S.C. §156 and 37 C.F.R. §§1.710-1.791, Applicant, SANOFI-AVENTIS, the address of which is 174 avenue de France, Paris FRANCE (hereinafter referred to as "Applicant,") represents that it is the owner and assignee of the entire interest in and to United States Patent No. 7,323,493 (Exhibit 1, "the '493 patent,") granted to Bernard Abramovici, Jean-Claude Gautier, Jean-Claude Gromenil, and Jean-Marie Marrier (hereinafter referred to as the "Inventors") for "SOLID PHARMACEUTICAL COMPOSITION CONTAINING BENZOFURAN DERIVATIVES" on January 29, 2008, by virtue of a name change from SANOFI-SYNTHELABO to Applicant, recorded July 22, 2005 at Reel 016345, Frame 0189.

12/08/2009 RLOGAN 00000001 181982 09446601

SANOFI-SYNTHELABO became assignee of record by virtue of an assignment from all of the Inventors recorded April 3, 2000 at Reel 010730, Frame 0992. (See Exhibit 2).

The '493 patent matured from Application No. 09/446,601, filed April 3, 2000.

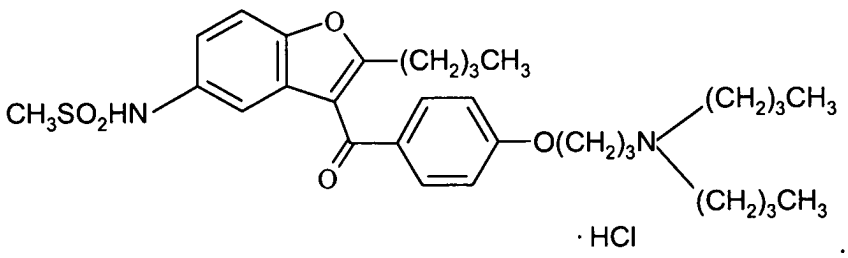
The approved product that is relevant to this application is MULTAQ® (dronedarone hydrochloride) 400 mg (base equivalent) tablets, referred to herein as "MULTAQ®" or "Approved Product".

The Marketing Applicant for MULTAQ® is sanofi-aventis U.S. LLC of 55 Corporate Drive, Bridgewater, New Jersey 08807, USA. A letter on behalf of the Marketing Applicant authorizing the patent owner to rely upon the activities of the Marketing Applicant, its predecessors, and affiliates is attached hereto as Exhibit 3.

The following information is submitted by Applicant, through its duly authorized attorney, in accordance with 35 U.S.C. §156 and the rules for extension of patent term issued by the USPTO at 37 C.F.R. Subpart F, §§1.710 to 1.791, and follows the numerical format set forth in 37 C.F.R. §1.740. The undersigned is authorized to act on behalf of Applicant and proper Power of Attorney has been submitted to and accepted by the USPTO (see Exhibit 4).

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved product is MULTAQ® (dronedarone hydrochloride) tablets for oral administration. Dronedarone hydrochloride has the chemical name N-{2-butyl-3-[4-(3-dibutylaminopropoxy)benzoyl]benzofuran-5-yl}methanesulfonamide, hydrochloride. The chemical structure of dronedarone hydrochloride is:



Dronedarone hydrochloride alternatively has the chemical name 2-n-butyl 3-[4-(3-di-n-butylamino-propoxy)benzoyl]5-methylsulfonamido benzofuran, hydrochloride.

MULTAQ® is the brand name for the approved product. It is currently prepared in tablet form for oral administration. The currently approved dosage form contains 400 mg (base equivalent) of dronedarone hydrochloride. In addition, each tablet currently contains the following excipients: hypromellose, starch, crospovidone, poloxamer 407, lactose monohydrate, colloidal silicon dioxide, magnesium stearate, polyethylene glycol 6000, titanium dioxide, and carnauba wax.

MULTAQ® is currently indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors, who are in sinus rhythm or who will be cadioverted. (A copy of the approved labeling is attached to the FDA's letter of approval, Exhibit 5).

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review period occurred:

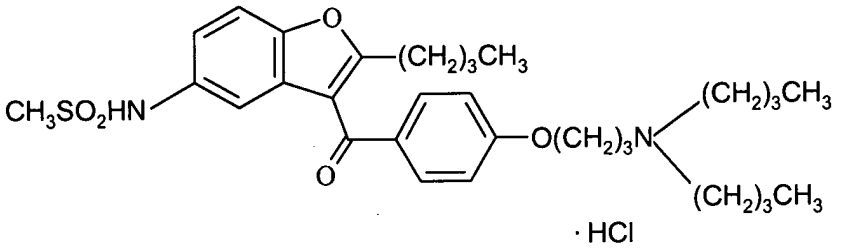
The approved product is a drug product and the submission was approved under Section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") (21 U.S.C. § 355(b)).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

Regulatory approval for MULTAQ® (dronedarone hydrochloride) tablets, based on NDA No. 22-425, was received on July 1, 2009. A copy of the letter from FDA setting forth such approval is attached hereto as Exhibit 5.

(4) An identification of each active ingredient in the product and as to each active ingredient a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act or the Virus-Serum-Toxin Act:

The sole active ingredient in the Approved Product is dronedarone hydrochloride, having the chemical structure:



Neither dronedarone hydrochloride nor any salt or any ester thereof has previously been approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act or the Virus-Serum-Toxin Act. In addition, Applicant notes that neither dronedarone nor any salt or ester of dronedarone has previously been approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act or the Virus-Serum-Toxin Act, and FDA has determined that MULTAQ® is entitled to five-year new chemical entity exclusivity.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to 37 CFR 1.720(f) and an identification of the date of the last day on which the application could be submitted:

This Application is timely filed, pursuant to 35 U.S.C. § 156(d)(1), within the permitted sixty-day (60-day) period that began on July 1, 2009 when the product received

permission under 21 U.S.C. § 355(b) and that will expire on August 30, 2009. Applicant understands that, pursuant to 37 C.F.R. § 1.720(f), the USPTO may deem this period to expire one day earlier, on August 29, 2009.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

1. **United States Patent Number**: 7,323,493
2. **Inventors**: Bernard Abramovici, Jean-Claude Gautier, Jean-Claude Gromenil, and Jean-Marie Marrier
3. **Issued**: January 29, 2008
4. **Expiration Date**: June 19, 2018

The expiration date of United States Patent No. 7,323,493 is June 19, 2018 based on the following: The '493 patent matured from Application No. 09/446,601, filed April 3, 2000 and is a 35 U.S.C. § 371 application of PCT/FR98/01285, filed June 19, 1998, which claims foreign priority to French Patent Application No. 97 07795 filed June 23, 1997. Thus, the earliest filing date under 35 U.S.C. §§ 120, 121 or 365 (c) for the '493 patent is June 19, 1998. The `493 patent term is 20 years from the earliest filing date under 35 U.S.C. §§ 120, 121 or 365 (c) (i.e., June 19, 1998). Therefore, the '493 patent will expire on June 19, 2018.

(7) A copy of the patent for which an extension is being sought:

A copy of the patent for which extension is sought, including the entire specification and claims, is attached hereto as Exhibit 1.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent:

United States Patent No. 7,323,493 is not subject to a terminal or statutory disclaimer.

United States Patent No. 7,323,493 has not been reexamined, and, thus, no reexamination certificate has been issued.

A copy of a Request for Certificate of Correction under 37 C.F.R. § 1.322, filed March 17, 2008 and a copy of a Certificate of Correction issued by the U.S. Patent and Trademark Office on July 22, 2008 is attached hereto as Exhibit 6.

The first (four year) maintenance fee for the '493 patent is not yet due. Attached as Exhibit 7 are a copy of a USPTO record confirming that no fees are currently due, a copy of a USPTO record showing that the window for the 4th year maintenance fee opens January 31, 2011, and a copy of a USPTO record showing when the 4th, 8th, and 12th year maintenance fees are due for the '493 patent. All records were downloaded from the USPTO website.

(9) A statement that the patent claims the approved product, a method of using the approved product, or a method of manufacturing the approved product and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on the approved product, method of using the approved product, or method of manufacturing the approved product:

The patent claims the approved product. Specifically, at least claims 1 to 3, 5 to 7, and 9 to 14 claim the approved product.

Pursuant to 37 C.F.R. § 1.740(a)(9), a showing which demonstrates the manner in which one product claim reads on the approved product is set forth herein below.

Claim 1 claims a solid pharmaceutical composition in tablet form for oral administration comprising a benzofuran derivative with antiarrhythmic activity selected from the group consisting of dronedarone and amiodarone, or a pharmaceutically

acceptable salt thereof, as an active principle, and a pharmaceutically acceptable nonionic hydrophilic surfactant selected from poloxamers, optionally in combination with one or more pharmaceutical excipients, said nonionic hydrophilic surfactant being present in a proportion of from 5% to 15% by weight of the active principle in base form, provided that the pharmaceutical composition does not contain a polysorbate surfactant.

Claim 1 covers the approved product, MULTAQ® (dronedarone hydrochloride) tablets, as follows:

- The approved MULTAQ® (dronedarone hydrochloride) product is a "solid pharmaceutical composition in tablet form for oral administration";
- The "benzofuran derivative with antiarrhythmic activity selected from the group consisting of dronedarone and amiodarone, or a pharmaceutically acceptable salt thereof, as an active principle" in MULTAQ® is dronedarone hydrochloride;
- The "pharmaceutically acceptable nonionic hydrophilic surfactant selected from poloxamers" in MULTAQ® is poloxamer 407;
- The "said nonionic hydrophilic surfactant being present in a proportion of from 5% to 15% by weight of the active principle in base form" is the poloxamer 407, as MULTAQ® (dronedarone hydrochloride) 400 mg tablets contain about 40 mg poloxamer 407 per tablet, which is 10% by weight of the dronedarone hydrochloride calculated in base form;
- MULTAQ® does not contain a polysorbate surfactant.

[CONTINUED ON NEW PAGE]

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. §156(g)

(i) For a patent claiming a human drug, antibiotic, or human biological product, the effective date of the Investigational New Drug application (IND) and the IND number, the date on which a New Drug Application (NDA) or a Product License Application (PLA) was initially submitted, and the NDA or PLA number; and the date on which the NDA was approved or the Product License Issued

An investigational new drug application ("IND") was filed on July 7, 1995, acknowledged as received on July 11, 1995, and assigned IND No. 48,344. A copy of the letter acknowledging receipt of the IND is attached as Exhibit 8. Accordingly, IND No. 48,344 became effective 30 days from July 11, 1995, which is August 10, 1995.

A second IND was filed on December 26, 1995, and assigned IND No. 49,484. A copy of the letter acknowledging receipt of the IND on December 26, 1995 is attached as Exhibit 9. Accordingly, IND No. 49,484 became effective 30 days from December 26, 1995, which is January 25, 1996.

An original new drug application ("NDA") was submitted on June 10, 2005 and acknowledged as received on June 10, 2005, in a letter from FDA dated July 19, 2005. (Exhibit 10). The NDA number assigned to this application for dronedarone hydrochloride was NDA 21-913. Accordingly, NDA 21-913 was submitted on June 10, 2005.

A subsequent new drug application ("NDA") was submitted on June 27, 2008 and acknowledged as received on July 31, 2008, in a letter from FDA dated August 6, 2008. (Exhibit 11). The NDA number assigned to this application for dronedarone hydrochloride was NDA 22-425. Accordingly, NDA 22-425 was submitted on July 31, 2008. The NDA was approved on July 1, 2009. (Exhibit 5).

[CONTINUED ON NEW PAGE]

(11) A brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

In accordance with 37 C.F.R. § 1.740(a)(11), a list of communications between the FDA and the Marketing Applicant, its predecessor, and affiliates, in IND Nos. 48, 344 and 49,484 and NDA Nos. 21-913 and 22-425 during the applicable regulatory review period with respect to the approved product is provided at Exhibits 12 and 13. The original sponsor of the original IND was Sanofi Recherche. Following a series of name changes and mergers, Sanofi Recherche is succeeded by sanofi-aventis U.S. LLC.

An IND was filed on July 7, 1995 and acknowledged as received on July 11, 1995 (which became effective on August 10, 1995). A second IND for a different formulation, which became the formulation ultimately approved, was filed on December 26, 1995 (which became effective on January 25, 1996).

Clinical trials were begun shortly following acceptance of the IND. The first clinical trial report was submitted on or about August 8, 1996. An End of Phase II meeting with the FDA was held on or about April 9, 2001. The first Phase III protocols were submitted to the FDA on or about September 12, 2001.

A first NDA was filed on June 10, 2005, and was assigned Application No. NDA 21-913. This NDA was found to be non-approvable by the FDA by letter dated August 29, 2006. On June 27, 2008, sanofi-aventis U.S. LLC submitted a complete response to the non-approvable letter in the form of an amendment to the NDA. The FDA then notified sanofi-aventis that the complete response was a new NDA because of a change in indication. The new NDA was acknowledged as received on July 31, 2008, and was

assigned Application No. 22-245. From July 31, 2008 through approval on July 1, 2009, sanofi-aventis U.S. LLC replied to multiple queries from the FDA.

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(12) A statement that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed including how the length of extension was determined:

(a) Statement of the eligibility of the patent for extension under 35 U.S.C. §156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. §156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product using the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) Pursuant to 35 U.S.C. §154 and for reasons discussed above, the term of United States Patent No. 7,323,493 is currently set to expire on June 19, 2018. This application is, therefore, being submitted prior to the expiration of the term of United States Patent No. 7,323,493.

(2) The term of this patent has never been extended under 35 U.S.C. §156(e)(1).

(3) This application is being submitted by Applicant, sanofi-aventis, the owner of record of United States Patent No. 7,323,493. (See Exhibit 2). Sanofi-

aventis is the owner of record by virtue of duly recorded assignments discussed above. This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty-day period beginning on July 1, 2009, the date the product received permission for marketing under Section 505 of the FFDCA [21 U.S.C. §355], and ending on August 30, 2009. Moreover, this application contains the information required under 35 U.S.C. §156(d).

(4) As evidenced by the July 1, 2009 letter from the FDA to sanofi-aventis U.S. LLC submitted as Exhibit 5, the product was subject to a regulatory review period under Section 505(b) of the FFDCA before its commercial marketing or use.

(5) The permission for the commercial marketing of the MULTAQ® (dronedarone hydrochloride) product is the first permitted commercial marketing and use under Section 505 of the FFDCA [21 U.S.C. §355] of the product, as defined in 35 U.S.C. § 156(f). (See Section 4, above).

(b) Statement as to length of extension claimed.

The term of U.S. Patent No. 7,323,493, now expiring June 19, 2018, should be extended to November 20, 2019, in accordance with 35 U.S.C. §156.

As set forth in 35 U.S.C. §156(g)(1), the regulatory review period equals the length of time between the effective date of IND No. 48,344 of August 10, 1995, and the submission of the NDA 21-913 on June 10, 2005 (i.e., the "testing phase"), a period of 3,592 days, plus the length of time between the submission of the NDA 21-913 on June 10, 2005 to NDA approval on July 1, 2009 (i.e., the "approval phase"), a period of 1,482 days. These two periods added together equal 5,074 days.

Pursuant to 37 C.F.R. § 1.775(d), the term of the patent as extended is determined by subtracting from the 5,074 day regulatory review period the following:

(i) 4,555 days, which is the number of days in the IND and NDA periods on or before the issuance of original United States Patent No. 7,323,493 on January 29, 2008; and

(ii) 0 days, which is one-half the number of days remaining in the IND period after the subtraction of 4,555 days above (wherein half days are ignored for purposes of this subtraction, as provided by 37 C.F.R. § 1.775(d)(1)(iii)).

From the foregoing calculation, an extension of 519 days results, i.e., the remaining period under 35 U.S.C. 156(g)(1)(B)(i) (0 days) plus the remaining period under 35 U.S.C. §156(g)(1)(B)(ii) (519 days). This length of an extension would provide a new expiration date for U.S. Patent No. 7,323,493 of November 20, 2019. However, this extension period is subject to two further potential limitations under 35 U.S.C. §156.

First, under 35 U.S.C. §156(g)(6)(A), a maximum extension of five years is permitted. In this case, since the current expiry date of U.S. Patent No. 7,323,493 is June 19, 2018, no patent term extension could extend the term of the patent beyond June 19, 2023. In this case, this provision does not operate to limit the possible extension available to U.S. Patent No. 7,323,493.

Second, under 35 U.S.C. §156(c)(3), if the calculated extension period would lead to a patent term that would result in a patent term exceeding 14 years after the date of approval, that is, a patent term expiring after July 1, 2023, the period of extension would be limited so that this period does not exceed 14 years. In this case, this provision does not operate to limit the possible extension available to U.S. Patent No. 7,323,493.

Accordingly, United States Patent No. 7,323,493 is eligible for 519 days patent term extension under 35 U.S.C. § 156.

(13) A statement that Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought (See 37 C.F.R. §1.765)

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension (See 37 C.F.R. §1.20(j))

The Director is hereby authorized to charge any fees due to this submission to our Deposit Account No. **18-1982**, under Docket No. IVD000703 US NP, for any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm), to prevent this application from being inadvertently abandoned. A duplicate of this Request (without Exhibits 1 to 13) is attached.

[CONTINUED ON NEW PAGE]

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed

John D. Conway
sanofi-aventis U.S. Inc.
US Patent Operations
Route #202-206 / P.O. Box 6800
MAIL CODE: BWD-303A
Bridgewater, NJ 08807-0800
Telephone: 908-231-3800
Telefax: 908-231-2626

Pursuant to 37 C.F.R. §1.740(b), this Request for Extension of Patent Term Under 35 U.S.C. §156, including Exhibits **1-13**, is accompanied by two additional copies, for a total submission of three copies.

Dated: August 18, 2009

Respectfully submitted,

By Kelly L. Bender

Kelly L. Bender
Registration No. 52,610
Attorney for Applicants

List of Exhibits Attached:

Exhibit 1	A copy of the U.S. Patent No. 7,323,493 for which extension is sought
Exhibit 2	A copy of the Patent Assignment Abstract
Exhibit 3	A letter of authorization from the NDA Holder, sanofi-aventis U.S. LLC
Exhibit 4	A copy of the submitted Revocation and New Power of Attorney
Exhibit 5	A copy of the NDA Approval Letter from the FDA
Exhibit 6	A copy of the Certificate of Correction and corresponding request
Exhibit 7	A copy of Patent Maintenance Fees Statement
Exhibit 8	A copy of letter of acknowledgment of IND 48,344 submission
Exhibit 9	A copy of letter of acknowledgment of IND 49,484 submission
Exhibit 10	A copy of letter of acknowledgment of NDA 21-913 submission
Exhibit 11	A copy of letter of acknowledgment of NDA 22-425 submission
Exhibit 12	Listing of the IND Events
Exhibit 13	Listing of the NDA Events

sanofi-aventis U.S. Inc.
US Patent Operations
Route #202-206 / P.O. Box 6800
MAIL CODE: BWD-303A
Bridgewater, NJ 08807-0800
Telephone: 908-231-3800; Telefax: 908-231-2626

EXHIBIT 1

US007323493B1

(12) **United States Patent**
Abramovici et al.

(10) **Patent No.: US 7,323,493 B1**
(45) **Date of Patent: Jan. 29, 2008**

(54) **SOLID PHARMACEUTICAL COMPOSITION CONTAINING BENZOFURAN DERIVATIVES**

(75) Inventors: **Bernard Abramovici**, Juvignac (FR); **Jean-Claude Gautier**, Clapiers (FR); **Jean-Claude Gromenil**, Mountbazin (FR); **Jean-Marie Marrier**, Lattes (FR)

(73) Assignee: **Sanofi-Aventis**, Paris (FR)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/446,601**

(22) PCT Filed: **Jun. 19, 1998**

(86) PCT No.: **PCT/FR98/01285**

§ 371 (c)(1),
(2), (4) Date: **Apr. 3, 2000**

(87) PCT Pub. No.: **WO98/58643**

PCT Pub. Date: **Dec. 30, 1998**

(30) **Foreign Application Priority Data**

Jun. 23, 1997 (FR) 97 07795

(51) **Int. Cl.**
A61K 31/343 (2006.01)

(52) **U.S. Cl.** **514/469**; 514/975; 514/960; 514/467

(58) **Field of Classification Search** 514/469, 514/467

See application file for complete search history.

(56) **References Cited**

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Primary Examiner—Ardin H. Marschel
Assistant Examiner—Donna Jagoe
(74) *Attorney, Agent, or Firm*—Kelly L. Bender

(57) **ABSTRACT**

The present invention relates to a solid pharmaceutical composition for oral administration characterized in that it comprises a benzofuran derivative with antiarrhythmic activity, or one of the pharmaceutically acceptable salts thereof, as an active principle, and a pharmaceutically acceptable nonionic hydrophilic surfactant optionally in combination with one or more pharmaceutical excipients.

14 Claims, 2 Drawing Sheets

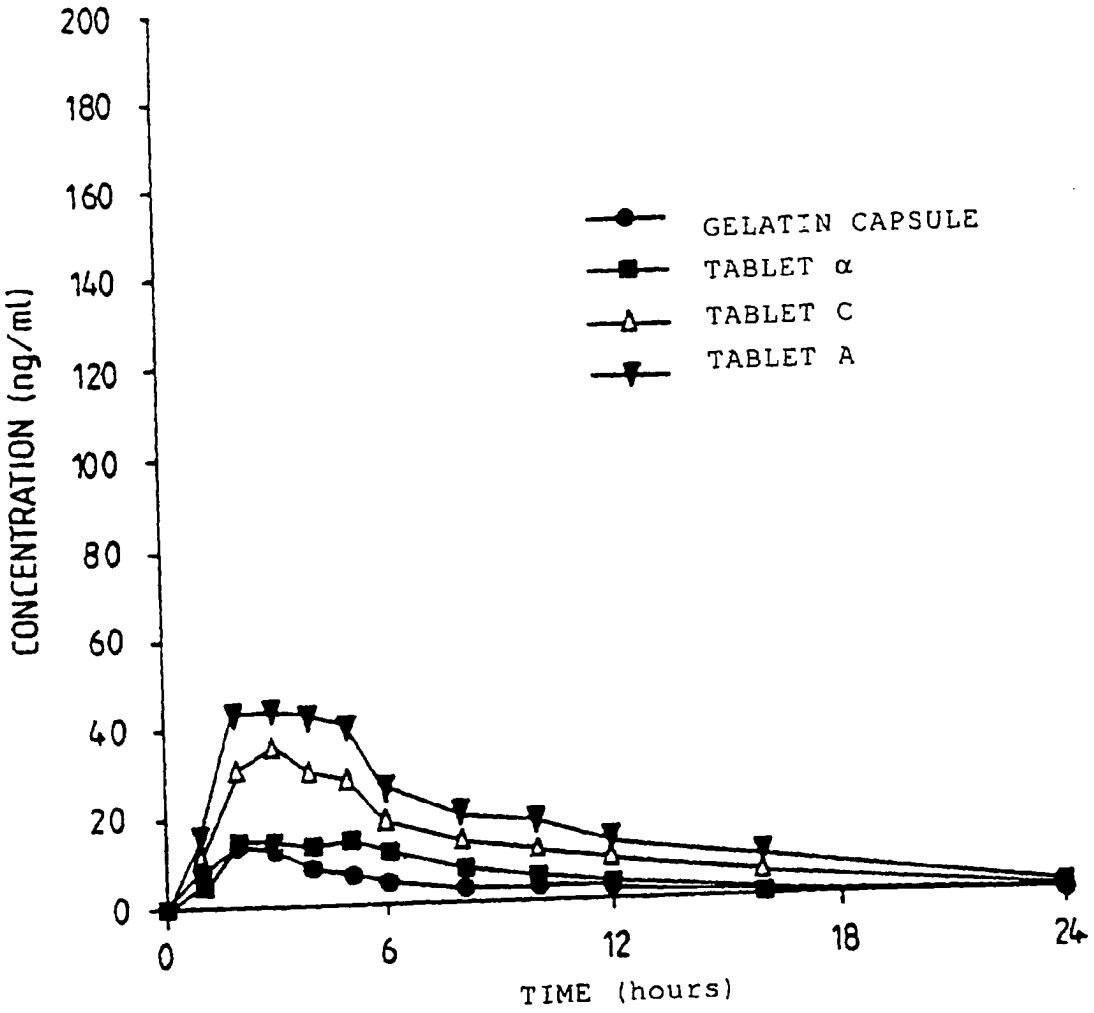
200
180
160
140
120
100
80
60
40
20
0
CONCENTRATION (ng/ml)
0
6
12
18
24
TIME (hours)
GELATIN CAPSULE
TABLET α
TABLET C
TABLET A

FIG. 1

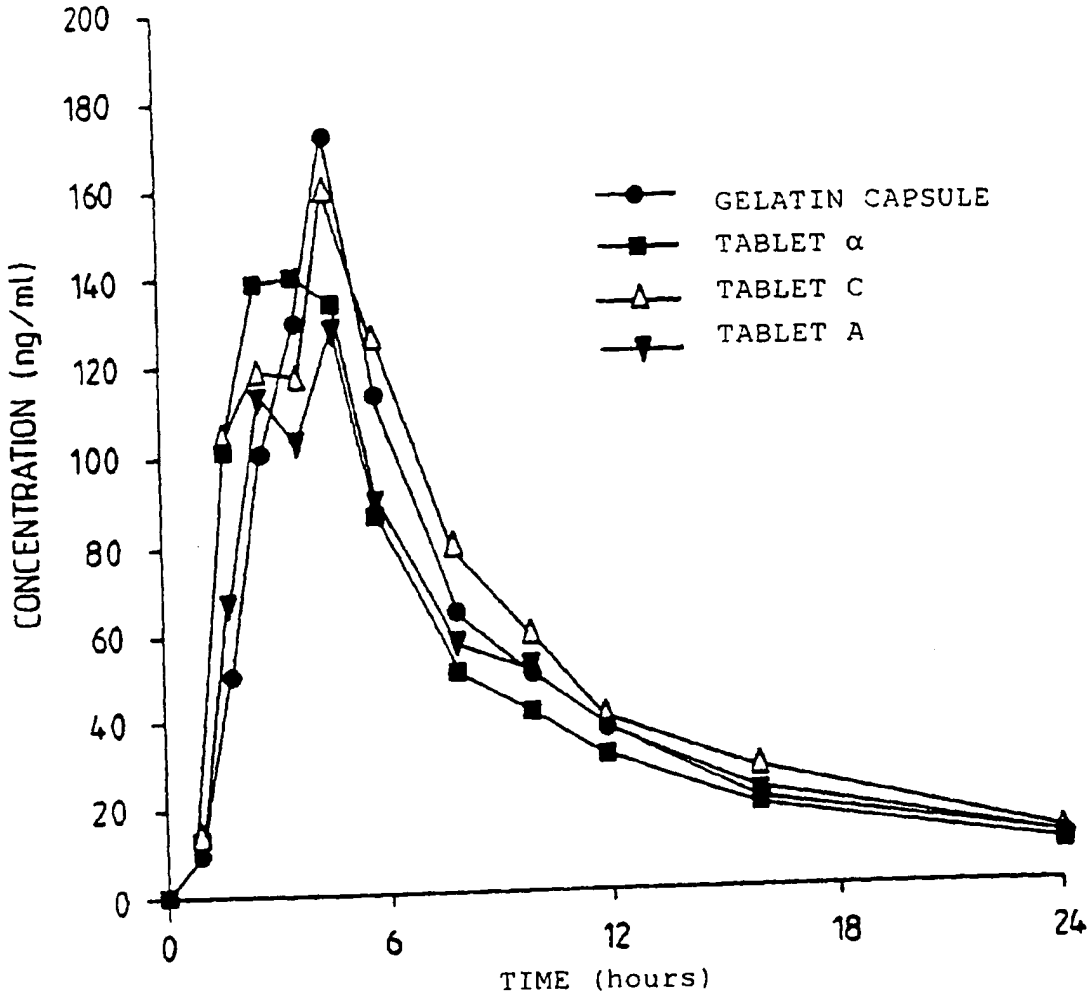
200
180
160
140
120
100
80
60
40
20
0
CONCENTRATION (ng/ml)
0
6
12
18
24
TIME (hours)
GELATIN CAPSULE
TABLET α
TABLET C
TABLET A

FIG. 2

SOLID PHARMACEUTICAL COMPOSITION CONTAINING BENZOFURAN DERIVATIVES

The present invention relates generally to a novel pharmaceutical composition for oral administration containing a benzofuran derivative as active principle.

More precisely, the invention relates to a solid pharmaceutical composition for oral administration containing a benzofuran derivative with anti-arrhythmic activity as active principle.

In the context of the present invention, the expression "benzofuran derivative with antiarrhythmic activity" is understood to denote a benzofuran compound chosen from those described in U.S. Pat. Nos. 3,248,401 and 5,223,510 and European patent EP 338,746, as well as in patent applications WO 88/07996, WO 89/02892, WO 90/02743 and WO 94/29289.

Of all of these compounds, mention may preferably be made of 2-n-butyl-3-[4-(3-di-n-butyl-aminopropoxy)benzoyl]-5-methylsulphonamidobenzofuran or dronedarone and the pharmaceutically acceptable salts thereof described in U.S. Pat. No. 5,223,510, as well as 2-n-butyl-3-(3,5-diiodo-4-diethylaminoethoxybenzoyl)-benzofuran or amiodarone and the pharmaceutically acceptable salts thereof described in U.S. Pat. No. 3,248,401.

Similarly, the expression "solid pharmaceutical composition" is understood to refer essentially to a pharmaceutical composition formed entirely of pulverulent solid ingredients which can be tabletted at room temperature, comprising the active principle and the excipients, these ingredients being essentially in powder form.

Consequently, the so-called semi-solid pharmaceutical compositions, formed of substances in pasty or waxy form when they are brought to moderate temperature (<70° C.), do not form part of the invention.

The antiarrhythmic compounds used in the context of the invention, in particular dronedarone and amiodarone in the form of their hydrochloride, are characterized by low solubility in aqueous medium.

For example, the solubility curve of dronedarone hydrochloride at room temperature and as a function of the pH reveals a maximum solubility around pH values of 3 to 5, of about 1 to 2 mg/ml, but very low solubility at pH values of about 6 to 7, since it is only 10 μg/ml at pH=7.

As regards amiodarone hydrochloride, its solubility at room temperature is from 0.3 to 0.9 mg/ml in the pH range from 3 to 4, and is a few μg/ml at pH=7.

Thus, it is possible to dissolve 400 mg of dronedarone hydrochloride in 200 ml of aqueous medium buffered to pH=4 (aqueous 0.1 M NaH_2PO_4 solution).

On the other hand, in this medium diluted to 1/10 with an aqueous solution buffered to pH=7 (aqueous 0.1 M Na_2HPO_4 solution), dronedarone hydrochloride precipitates (pH of the final medium: 6.7).

Since these solubility conditions are similar to those recorded in the gastrointestinal tract, it can be assumed that dronedarone hydrochloride risks being subjected, in the stomach, to acidic conditions which are favourable to its solubilization, but, on the other hand, risks encountering a medium of pH=6 to 7 once it enters the intestine, i.e. a non-solubilizing medium in which it will precipitate.

This behaviour in intestinal medium probably makes it possible to explain in vivo the low bio-availability of dronedarone hydrochloride and the differences observed after administration with or without food, since it has been observed that the bio-availability of dronedarone hydrochloride in dogs and in man is increased after the intake of food, in particular fats, which can greatly modify the precipitation kinetics of this active principle and also help to place it in emulsion form.

Since the absorption of food gives rise to the secretion of bile salts, which are anionic surfactants, it appears that this might have a favourable influence on the solubilization of dronedarone hydrochloride.

However, tests carried out to this end showed, in contrast, that this active principle precipitates in the presence of bile salts such as sodium taurocholate.

The development of an oral pharmaceutical composition of dronedarone, of amiodarone or of pharmaceutically acceptable salts thereof, which is capable of avoiding the precipitation of the active principle in neutral medium and of reducing the variability of absorption of this active principle into the plasma, i.e. of providing an acceptable bioavailability independently of the presence of food, remains of fundamental interest.

It has now been found, surprisingly, that the combination of a nonionic hydrophilic surfactant with dronedarone, amiodarone or the pharmaceutically acceptable salts thereof, makes it possible to maintain the solubilization of this active principle in neutral medium and to reduce, in man, its variability of absorption into the blood.

This observation is all the more surprising since preliminary tests carried out on dogs did not make it possible to show that a nonionic hydrophilic surfactant was capable of increasing the fasted bioavailability of dronedarone hydrochloride, and at the same time of reducing the variability of absorption of this active principle into the plasma.

Thus, the invention relates to a solid pharmaceutical composition for oral administration comprising a benzofuran derivative with antiarrhythmic activity, or one of the pharmaceutically acceptable salts thereof, as an active principle, and to a pharmaceutically acceptable nonionic hydrophilic surfactant optionally in combination with one or more pharmaceutical excipients.

This pharmaceutical composition can be in any solid pharmaceutical form which is suitable for oral administration, such as a tablet which may or may not be splittable, a granule, a gelatin capsule or a powder in a unit sachet.

Consequently, another subject of the invention relates to the above oral pharmaceutical composition in tablet, granule, gelatin capsule or powder form.

The nonionic hydrophilic surfactant used in the composition of the invention can be chosen from:

- ethyleneoxide/propyleneoxide copolymers referred to hereinbelow as poloxamers, such as poloxamer 124 sold under the brand name Synperonic® PE/L44; poloxamer 188 sold under the brand name Pluronic® F68 or Synperonic® PE/F68; poloxamer 237 sold under the brand name Pluronic® F87 or Synperonic® PE/F87; poloxamer 338 sold under the brand name Synperonic® PE/F108 or poloxamer 407 sold under the brand name Pluronic® F127, Synperonic® PE/F127 or Lutrol® F127.
- polyethoxylated castor oils such as those sold under the brand name Cremophor® RH40.
- ethoxylated polysorbates, such as polysorbate 20, polysorbate 40, polysorbate 60 and polysorbate 80 sold respectively under the brand names Tween® 20, Tween® 40, Tween® 60 and Tween® 80.
- or alternatively polyethylene hydroxystearates such as polyethylene hydroxystearate 660 sold under the brand name Solutol® HS15.

As preferred surfactant, mention may be made of poloxamer 407.

Usually, the nonionic hydrophilic surfactant in question is incorporated into the solid compositions of the invention in a proportion of from 1% to 50% by weight relative to the active principle in base form, irrespective of the unitary or non-unitary pharmaceutical form adopted for packaging them.

For the preparation of solid compositions in tablet form or packaged in gelatin capsule form, from 1% to 20% by weight of surfactant relative to the active principle in base form, preferably from 5% to 15%, will be used, for example.

As a non-limiting guide, the amount of active principle can range from 50 to 500 mg per administration unit in tablet form, which entails the incorporation of an amount of surfactant of between 0.5 and 100 mg. These amounts of surfactant prove to be perfectly acceptable with pharmaceutical forms such as tablets or gelatin capsules, whose sizes will remain compatible with oral administration.

In a preferred manner, solid pharmaceutical compositions of the invention, for example in tablet or gelatin capsule form, can contain from 200 to 400 mg of active principle calculated in the form of base and from 5% to 15%, more particularly 10%, by weight of nonionic hydrophilic surfactant relative to the active principle in base form.

For packaging in the form of powder in a unit sachet, from 1% to 50% by weight of nonionic hydrophilic surfactant relative to the active principle in base form may be used.

Besides the surfactant in question, the compositions in solid form according to the invention will comprise other pharmaceutical excipients generally used in the development of oral pharmaceutical forms.

These substances are entirely known to those skilled in the art, who can readily select them depending on the type of oral composition chosen.

As nonlimiting examples, mention may be made of binders, generally cellulose derivatives such as methylcellulose, hydroxyethylcellulose or methyl-hydroxypropylcellulose, or alternatively macrogols such as macrogol 6000; flow agents such as colloidal silica; vinylpyrrolidone polymers or copolymers such as polyvinylpyrrolidone; diluents such as lactose or mannitol; starches such as wheat starch or corn starch; lubricants such as magnesium stearate or sodium stearyl fumarate.

The compositions of the invention can be prepared by carrying out known processes involving, in particular, techniques of granulation via a wet or dry route, via fusion or via direct tabletting for the formation of tablets.

For example, tablets can be prepared by wet granulation by mixing together, at the initial stage, all of the ingredients, including the active principle and the surfactant, except for, however, the lubricant.

Operations of wetting with purified water, drying and sizing of the granule obtained, lubrication and tabletting or direct filling of gelatin capsules are then carried out.

According to variants of this method:

a) all of the ingredients, including the active principle, except for the surfactant and the lubricant, are mixed together at the initial stage and the process continues by operations of wetting with an aqueous solution of the surfactant, granulation, drying, sizing, lubrication and tabletting or direct filling of gelatin capsules,

or

b) all of the ingredients, including the active principle and the surfactant, except for the binder and the lubricant, are mixed together at the initial stage and the process then continues by operations of wetting with an aqueous solution of the binder, granulation, drying, sizing, lubrication and tabletting or direct filling of gelatin capsules.

These methods can also be modified by including a continuous granulation process which uses the fluidized airbed technique at the stage of the wetting operation.

In addition, it is also possible to use a process in which all of the ingredients are mixed together in the initial stage, except for the lubricant, which is heated to a temperature of about 60° C. to 65° C. Operations of hot granulation, sizing after cooling, lubrication and tabletting or direct filling of gelatin capsules are then carried out.

According to dry granulation techniques, all of the ingredients, including the active principle and the surfactant, except for the lubricant, are first mixed together and the process then continues with operations of screening, compacting, sizing, lubrication and tabletting or direct filling of gelatin capsules.

Finally, the process can be performed by direct tabletting using the following sequence of operations: mixing of the ingredients including the active principle and the surfactant, except the lubricant, followed by screening and mixing, then lubrication and finally tabletting or direct filling of gelatin capsules.

The characteristics and advantages of the oral compositions according to the invention will become apparent in the light of the description hereinbelow using specific oral compositions given by way of example with reference to the attached drawings.

I. Test of Maintenance in Solution at pH=6.7

A. Active Principle Alone

Solutions were prepared containing 2 mg/ml of dronedarone hydrochloride in hydrogenphosphate (NaH_2PO_4) buffered medium at pH=4.5 for 2 hours at 37° C. in the presence or absence of x % of nonionic hydrophilic surfactant to be studied, calculated on a weight basis relative to the active principle in base form.

This solution was then diluted to 1/10th in a neutral phosphate medium ($Na_{2\ HPO4}$+NaH_2PO_4), the pH of the final solution being 6.7.

After 2 hours at 37° C., the solution was filtered through an Acrodisc® brand 5 μm filter and the active principle in solution was assayed by UV spectrometry.

Surfactant	x %	% of dronedarone hydrochloride in solution
TWEEN ® 20	50	65
TWEEN ® 40	50	63
TWEEN ® 60	50	74
TWEEN ® 80	50	69
Synperonic ® PE/F68	50	74
Synperonic ® PE/F87	50	75
Synperonic ® PE/F127	50	95
CREMOPHOR ® RH 40	50	64
SOLUTOL ® HS 15	50	59
Synperonic ® PE/F127	10	78
Synperonic ® PE/F127	5	63
—	—	5

B. Active Principle in Tablet Form

Solutions were prepared containing 2 mg/ml of dronedarone hydrochloride (expressed in base form) in hydrogenphosphate (NaH_2PO_4) buffered medium at pH=4.5 or containing 2 mg/ml of amiodarone hydrochloride, in a buffered medium at pH=3.5.

These solutions were obtained by dissolving dronedarone hydrochloride tablets or amiodarone hydrochloride tablets containing or not containing 10% of poloxamer 407 (Synperonic® PE/F127), i.e.:

	Tablets	
	α (mg)	A (mg)
Dronedarone hydrochloride (corresponding to 400 mg of base)	426	426
Methylhydroxypropylcellulose	12	12
Lactose monohydrate	63.6	63.6
Modified corn starch	60	60
Polyvinylpyrrolidone	30	30
Anhydrous colloidal silica	2.4	2.4
Synperonic ® PE/F127	—	40
Magnesium stearate	6	6
	600	640

	Tablets	
	β (mg)	B (mg)
Amiodarone hydrochloride	200	200
Lactose monohydrate	71	71
Modified corn starch	66	66
Crosslinked polyvinylpyrrolidone	6	6
Anhydrous colloidal silica	2.4	2.4
Synperonic ® PE/F127	—	20
Magnesium stearate	4.6	4.6
	350	370

After 2 hours of dissolution at 37° C., these solutions are diluted to 1/10th in a neutral phosphate medium (Na_2HPO_4+NaH_2PO_4), the pH of the final solution being 6.7.

The test was then continued as described in paragraph A above and the following results were obtained:

	% of dronedarone hydrochloride in solution
Tablet α	4.6
Tablet A	80

	% of amiodarone hydrochloride in solution
Tablet β	55
Tablet B	100

These results show that, in tablets, the incorporation of 10% by weight of poloxamer 407, relative to the base dronedarone or to the amiodarone hydrochloride, makes it possible to maintain from 80% to 100% of active principle in solution for 2 hours.

II. Pharmacokinetic Tests

Comparative tests with dronedarone hydrochloride were carried out on 16 male volunteers, 8 of whom had been fasted and the other 8 not.

These tests were performed using tablets of the invention: one at 10% by weight of surfactant relative to the weight of dronedarone in base form (tablet A above), the other at 5% by weight of the same surfactant (tablet C below), i.e.:

Tablet C	mg
Dronedarone hydrochloride (corresponding to 400 mg of base)	426
Methylhydroxypropylcellulose	12
Lactose monohydrate	63.6
Modified corn starch	60
Polyvinylpyrrolidone	30
Anhydrous colloidal silica	2.4
Synperonic ® PE/F127	20
Magnesium stearate	6
	620

compared with compositions free of nonionic hydrophilic surfactant, i.e.:

a) tablet α above

b) gelatin capsule having a composition of formulation:

	mg
Dronedarone hydrochloride (corresponding to 200 mg of base)	213
Modified corn starch	86.2
Lactose monohydrate	129.2
Talc	48
Anhydrous colloidal silica	1.2
Magnesium stearate	2.4
	480

Each of these volunteers received a single dose of dronedarone hydrochloride equivalent to 800 mg of base in the form of the above gelatin capsule, of tablet α, of tablet A or of tablet C, each single dose being separated from the following one by an interval of 7 days.

Plasmatic dronedarone assays were then carried out on each individual 0, 1, 2, 3, 4, 5, 6, 7, 10, 12, 16 and 24 hours after administration and the maximum concentrations of this active principle (C max in ng/ml) were noted, as well as the area under the curves defined by the concentration of the active principle as a function of time (AUC in ng.h/ml).

This procedure was repeated in a second series of tests carried out on the same two groups of 8 alternate volunteers, i.e. the 8 fasted volunteers carrying out the test while not fasted, and vice versa.

BRIEF DESCRIPTION OF THE DRAWINGS

The results obtained when fasted are reproduced in the attached FIG. 1 and those obtained while not fasted appear in the attached FIG. II, in which:

a) the curve referred to as "gelatin capsule" represents the average plasmatic concentration obtained with the composition in the form of a gelatin capsule

b) the curve referred to as "tablet α" represents the average plasmatic concentration obtained with the tablet α

c) the curve referred to as "tablet A" represents the average plasmatic concentration obtained with the tablet A containing 10% of Synperonic® PE/F127 surfactant

d) the curve referred to as "tablet C" represents the average plasmatic concentration obtained with tablet C containing 5% of Synperonic® PE/F127 surfactant.

From these curves, it is possible in particular:

1) to deduce that the presence of the surfactant increases the fasted bioavailability of the active principle.
2) to draw up the following comparative tables from the results of the C max and AUC values obtained with each formulation in the non-fasted volunteers compared with the corresponding results in the fasted volunteers, relative to 1:

TABLE I

	Treatment			
Ratio of the C max values	Gelatin capsule	Tablet α	Tablet C	Tablet A
Fasted	1	1	1	1
Not fasted	12.5	10.3	4.8	2.7

TABLE II

	Treatment			
Ratio of the AUC values	Gelatin capsule	Tablet α	Tablet C	Tablet A
Fasted	1	1	1	1
Not fasted	16.7	8.9	5.3	3.2

These tables show that the surfactant is capable of reducing by a factor of 2 to 5 the variations in maximum plasmatic concentrations of active principle obtained in non-fasted individuals compared with fasted individuals (Table I).

Similarly, it may be concluded that the large variations in bioavailability recorded with surfactant-free compositions could be reduced by a factor of 1.5 to 5 (Table II).

The following non-limiting examples illustrate the invention.

EXAMPLE 1

Dronedarone Hydrochloride Tablet

Dronedarone hydrochloride tablets of the formulation below were prepared:

Ingredients	mg	%
Dronedarone hydrochloride (corresponding to 400 mg of base)	426	65.5
Methylhydroxypropylcellulose	21.1	3.25
Lactose monohydrate	46.55	7.2
Modified corn starch	45.5	7
Polyvinylpyrrolidone	65	10
Poloxamer 407	40	6.15
Anhydrous colloidal silica	2.6	0.4
Magnesium stearate	3.25	0.5
	650	100

by applying the process below:

After screening, 724.2 g of dronedarone hydrochloride, 35.9 g of methylhydroxypropylcellulose, 79.1 g of lactose monohydrate, 77.4 g of corn starch and 82.9 g of polyvinylpyrrolidone are mixed together.

The mixture is moistened with 68 g of poloxamer 407 (Synperonic® PE/F127) as a solution in 408 g of purified water, and this mixture is granulated. The wet mass is dried at a temperature of about 50° C. and is sized on screens with a mesh size of 1.250 mm. 27.6 g of polyvinylpyrrolidone, 4.4 g of anhydrous colloidal silica and 5.5 g of magnesium stearate are mixed with the granule thus sized and the final mixture is then tabletted in a proportion of 650 mg per unit.

EXAMPLE 2

Dronedarone Hydrochloride Tablet

Dronedarone hydrochloride tablets of identical formulation to that of Example 1 were prepared by applying the process below:

After screening, 724.2 g of dronedarone hydrochloride, 35.9 g of methylhydroxypropylcellulose, 79.1 g of lactose monohydrate, 77.4 g of corn starch, 82.9 g of polyvinylpyrrolidone and 68 g of poloxamer 407 (Synperonic® PE/F127) are mixed together. The mixture is then moistened with purified water, after which the process is carried out in the same way as in Example 1 in order to obtain tablets with a weight of 650 mg per unit.

EXAMPLE 3

Dronedarone Hydrochloride Tablet

Dronedarone hydrochloride tablets of identical formulation to that of Example 1 were prepared by applying the process below:

After screening, 724.2 g of dronedarone hydrochloride, 79.1 g of lactose monohydrate, 77.4 g of corn starch, 82.9 g of polyvinylpyrrolidone and 68 g of poloxamer 407 (Synperonic® PE/F127) are mixed. The mixture is moistened with 35.9 g of methylhydroxypropylcellulose as a solution in 408 g of purified water and this mixture is granulated. The wet mass is dried at a temperature of about 50° C. and is sized on a screen with a mesh size of 1.250 mm. 27.6 g of polyvinylpyrrolidone, 4.4 g of anhydrous colloidal silica and 5.5 g of magnesium stearate are mixed with the granule thus sized and the final mixture is then tabletted in a proportion of 650 mg per unit.

EXAMPLE 4

Dronedarone Hydrochloride Tablet

Dronedarone hydrochloride tablets of the formulation below were prepared:

Ingredients	mg	%
Dronedarone hydrochloride (corresponding to 400 mg of base)	426	65.5
Microcrystalline cellulose	65	10
Anhydrous colloidal silica	2.6	0.4
Anhydrous lactose	42.65	6.6
Polyvinylpyrrolidone	13	2
Poloxamer 407	40	6.15
Macrogol 6000	57.5	8.85
Magnesium stearate	3.25	0.5
	650	100

by carrying out the process below:

After screening, 724.2 g of dronedarone hydrochloride, 110.5 g of microcrystalline cellulose, 2.2 g of anhydrous colloidal silica, 72.5 g of anhydrous lactose, 22.1 g of polyvinylpyrrolidone, 68 g of poloxamer 407 (Synperonic® PE/F127) and 97.8 g of macrogol 6000 are mixed together. The temperature of the mixture is raised to 65° C. in a thermostatically-controlled tank, with slow stirring. This mixture is granulated with fast stirring, cooled to room temperature and then sized. 2.2 g of anhydrous colloidal

silica and 5.5 g of magnesium stearate are then mixed with the sized granule and the final mixture is tabletted in a proportion of 650 mg per unit.

This granulation process can also be carried out in apparatus with a fluidized airbed.

EXAMPLE 5

Dronedarone Hydrochloride Tablet

Dronedarone hydrochloride tablets of identical formulation to that of Example 4 were prepared by applying the process below:

After sizing, 724.2 g of dronedarone hydrochloride, 110.5 g of microcrystalline cellulose, 2.2 g of anhydrous colloidal silica, 72.5 g of anhydrous lactose, 22.1 g of polyvinylpyrrolidone, 68 g of molten poloxamer 407 (Synperonic® PE/F127) and 97.8 g of molten macrogol 6000 are mixed together.

The process is then carried out in the same way as in Example 4, in order to obtain tablets with a weight of 650 mg per unit.

EXAMPLE 6

Dronedarone Hydrochloride Tablet

Dronedarone hydrochloride tablets of identical formulation to that of Example 4, but after replacing the macrogol 6000 with an equivalent amount of poloxamer 407, were prepared by applying the process below:

After sizing, 724.2 g of dronedarone hydrochloride, 110.5 g of microcrystalline cellulose, 2.2 g of anhydrous colloidal silica, 72.5 g of anhydrous lactose, 22.1 g of polyvinylpyrrolidone and 166.7 g of poloxamer 407 (Synperonic® PE/F127) are mixed together.

The process is then performed in the same way as in Example 4, in order to obtain tablets with a weight of 650 mg per unit.

EXAMPLES 7 and 8

Following the processes described above, tablets of the formulation below were prepared:

a)

Ingredients	mg	%
Dronedarone hydrochloride (corresponding to 400 mg of base)	426	65.6
Microcrystalline cellulose	26	4
Corn starch	45.5	7
Polyvinylpyrrolidone	65	10
Poloxamer 407	40	6.1
Anhydrous colloidal silica	2.6	0.4
Magnesium stearate	3.25	0.5
Lactose monohydrate	41.65	6.4
	650	100

b)

Ingredients	mg	%
Dronedarone hydrochloride (corresponding to 200 mg of base)	213	65.6
Microcrystalline cellulose	13	4
Corn starch	22.75	7
Polyvinylpyrrolidone	32.5	10
Poloxamer 407	20	6.1
Anhydrous colloidal silica	1.3	0.4
Magnesium stearate	1.625	0.5
Lactose monohydrate	20.825	6.4
	325	100

The invention claimed is:

1. A solid pharmaceutical composition in tablet form for oral administration comprising a benzofuran derivative with antiarrhythmic activity selected from the group consisting of dronedarone and amiodarone, or a pharmaceutically acceptable salt thereof, as an active principle, and a pharmaceutically acceptable nonionic hydrophilic surfactant selected from poloxamers, optionally in combination with one or more pharmaceutical excipients, said nonionic hydrophilic surfactant being present in a proportion of from 5% to 15% by weight of the active principle in base form, provided that the pharmaceutical composition does not contain a polysorbate surfactant.

2. A pharmaceutical composition according to claim 1 wherein the pharmaceutically acceptable salt is the hydrochloride.

3. A pharmaceutical composition according to claim 2, wherein the benzofuran derivative is dronedarone hydrochloride.

4. A pharmaceutical composition according to claim 2, wherein the benzofuran derivative is amiodarone hydrochloride.

5. A pharmaceutical composition according to claim 1 wherein the nonionic hydrophilic surfactant is selected from the group consisting of poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, and poloxamer 407.

6. A pharmaceutical composition according to claim 5 wherein the nonionic hydrophilic surfactant is poloxamer 407.

7. A pharmaceutical composition according to claim 6 wherein the benzofuran derivative is dronedarone hydrochloride.

8. A pharmaceutical composition according to claim 6 wherein the benzofuran derivative is amiodarone hydrochloride.

9. A pharmaceutical composition according to claim 5 containing from 50 to 500 mg of active principle.

10. A pharmaceutical composition according to claim 9, containing from 200 to 400 mg of active principle.

11. A pharmaceutical composition according to claim 10, containing from 200 to 400 mg of active principle, calculated in base form, and 10% by weight of nonionic hydrophilic surfactant relative to the active principle in base form.

12. A pharmaceutical composition according to claim 11 wherein the active principle is selected from the group consisting of amiodarone hydrochloride and dronedarone hydrochloride or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition according to claim 12 wherein the nonionic hydrophilic surfactant is poloxamer 407.

14. A pharmaceutical composition according to claim 13 wherein the active principle is dronedarone hydrochloride.

* * * * *

EXHIBIT 2

Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 2

Patent #: 7323493 **Issue Dt:** 01/29/2008 **Application #:** 09446601 **Filing Dt:** 04/03/2000

Inventors: JEAN-CLAUDE GAUTIER, JEAN-CLAUDE GROMENIL, JEAN-MARIE MARRIER, BERNARD ABRAMOVICI

Title: SOLID PHARMACEUTICAL COMPOSITIONS CONTAINING BENZOFURANE DERIVATIVES

Assignment: 1

Reel/Frame: 010730/0992 **Recorded:** 04/03/2000 **Pages:** 3

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors: ABRAMOVICI, BERNARD — **Exec Dt:** 03/13/2000
GAUTIER, JEAN-CLAUDE — **Exec Dt:** 03/13/2000
GROMENIL, JEAN-CLAUDE — **Exec Dt:** 03/13/2000
MARRIER, JEAN-MARIE — **Exec Dt:** 03/12/2000

Assignee: SANOFI-SYNTHELABO
174 AVENUE DE FRANCE
75013 PARIS, FRANCE

Correspondent: SANOTI-SYNTHELABO INC.
MICHAEL D. ALEXANDER
PATENT DEPARTMENT
9 GREAT VALLEY PKWY
MALVERN, PA 19355

Assignment: 2

Reel/Frame: 016345/0189 **Recorded:** 07/22/2005 **Pages:** 16

Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

Assignor: SANOFI-SYNTHELABO — **Exec Dt:** 08/20/2004

Assignee: SANOFI-AVENTIS
174 AVENUE DE FRANCE
PARIS, FRANCE 75013

Correspondent: ROSS J. OEHLER
ROUTE #202-206/P.O. BOX 6800
MAIL CODE: D303-A
BRIDGEWATER, NJ 08807

Search Results as of: 07/08/2009 05:00 AM

If you have any comments or questions concerning the data displayed, contact PRD / Assignments at 571-272-3350.
Web interface last modified: October 18, 2008 v.2.0.2

EXHIBIT 3

John D. Conway
Vice President
US Patent Operations

August 13, 2009

sanofi-aventis
174 Avenue de France
Paris, FRANCE

Re: Application for Extension of U.S. Patent No. 7,323,493

To Whom It May Concern:

On behalf of sanofi-aventis U.S., LLC, Marketing Applicant for New Drug Application No. 22-425 for MULTAQ® (dronedarone hydrochloride) Tablets 400 mg, I hereby authorize the patent owner of record, sanofi-aventis, in connection with its application for extension of U.S. Patent No. 7,323,493, to rely upon the activities of sanofi-aventis U.S., LLC, and its predecessors and affiliates, undertaken in connection with seeking approval by the Food and Drug Administration of NDA No. 22-425. Sanofi-aventis U.S., LLC is a wholly owned subsidiary of sanofi-aventis and henceforth the activities of the marketing applicant is permitted under the patent.

Sincerely yours,

John D. Conway
Vice President
US Patent Operations
sanofi-aventis U.S., LLC
1041 Route 202-206
Bridgewater, NJ 08807

Mail Code: BRW D-203A, 1041 Route 202-206, PO Box 6800, Bridgewater, NJ 08807
Tel. : (908) 231-3364; Fax : (908) 231-2626; E-mail: John.Conway@sanofi-aventis.com
www.sanofi-aventis.com

EXHIBIT 4

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TO THE UNITED STATES PATENT OFFICE

Applicants Docket Number:
IVD994 US PCT

Applicants:
B. Abramovici et al.

Serial No.
09/446,601

Filing Date:
April 3, 2000

Title of Invention:
Solid Pharmaceutical Compositions Containing Benzofuran Derivatives

CERTIFICATE OF TRANSMISSION
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Signature Della Coughlin

Total Number of Pages Sent: 3

Attorney: **Paul R. Darkes**

Group Art Unit: **1614**
Examiner: **D. Jagoe**

TO: Mail Stop
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Please acknowledge receipt of the below-listed documents for the above Application by return telefax to (908) 231-2626. If any fees are required, please charge our deposit account (18-1982) in the name of **Aventis Pharmaceuticals Inc.**

- ☐ Amendment, 37 CFR _____
- ☐ Charge deposit account, in duplicate
- ☐ Extension of Time Petition
- ☐ Issue Fee Transmittal & Advance Order
- ☐ Maintenance Fee Transmittal
- ☐ Fee Transmittal
- ☐ Petition under 37 CFR _____
- ☒ Other Revocation of Power of Attorney with New Power of Attorney and Change of Correspondence Address
- ☒ Other Statement Under 37 CFR 3.73 (b)
- ☐ Other

NOTICE: The documents accompanying this telecopy transmission are intended only for the use of the individual or entity named above. If you have received this telecopy in error, please immediately notify the sender by telephone to arrange for the return of the original documents.

PAGE 1/3 * RCVD AT 3/28/2005 2:32:44 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/6 * DNIS:8729306 * CSID:908 231 2626 * DURATION (mm-ss):01-12

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PTO/SB/82 (08-04)
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REVOCATION OF POWER OF ATTORNEY WITH NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	09/446,601
Filing Date	April 3, 2000
First Named Inventor	ABRAMOVICI, et al.
Art Unit	1614
Examiner Name	D. Jagoe
Attorney Docket Number	IVD994 US PCT

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☑ I hereby appoint the practitioners associated with the Customer Number: 005487

☐ Please change the correspondence address for the above-identified application to:

☑ The address associated with Customer Number: 005487

OR

☐ Firm *or* Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Fax			

I am the:

☐ Applicant/Inventor.

☑ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Signature			
Name	Elisabeth THOURET-LEMAITRE		
Date	Directeur Brevets / Patent Director	Telephone	

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.36. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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CENTRAL FAX CENTER
MAR 28 2005

PTO/SB/96 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: SANOFI-SYNTHELABO

Application No./Patent No.: 09/446,601 Filed/Issue Date: April 2, 2000

Entitled: Solid Pharmaceutical Compositions Benzofuran Derivatives

SANOFI-SYNTHELABO, a French corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☑ the assignee of the entire right, title, and interest; or

2. ☐ an assignee of less than the entire right, title and interest.
The extent (by percentage) of its ownership interest is _____ %

in the patent application/patent identified above by virtue of either:

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 010730, Frame 0992, or for which a copy thereof is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

☐ Copies of assignments or other documents in the chain of title are attached.
[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature Date

Elisabeth THOURET-LEMARRE
Directeur Brevets / Patent Director
Printed or Typed Name Telephone Number

Title

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

EXHIBIT 5

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-425

NDA APPROVAL

sanofi-aventis U.S., LLC
Attention: Marsha Miller, Ph.D.
Assistant Director, Regulatory Development
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Miller:

Please refer to your new drug application (NDA) dated June 27, 2008, received July 31, 2008, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Multaq (dronedarone hydrochloride) Tablets 400 mg.

We acknowledge receipt of your submissions dated August 14, 15, October 17, 27, 31, November 3, 10, 11, 14, 20, December 2, 3, 10, 17, 19, 24, 2008, and January 22, 28, , 30, February 5, 9, 13, 19, 23, 26, 27, March 10, April 3, 24, 29, May 1, 4, 5, 18, 19, June 4, 10, and 25, 2009.

This new drug application provides for the use of Multaq (dronedarone hydrochloride) Tablets to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors (i.e., age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥50 mm or left ventricular ejection fraction [LVEF] <40%), who are in sinus rhythm or who will be cardioverted.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-425.**" Approval of this submission by FDA is not required before the labeling is used.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the submitted carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper

copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-425.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because of the rarity of AF/AFL in the pediatric population, the geographical dispersion of such patients, and the disparate causes of the condition in such patients.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of lung toxicity, severe skin reactions, or neuropathies, all concerns raised by the effect of the related molecule amiodarone, or to identify use of Multaq (dronedarone hydrochloride) in patients for whom its use is contraindicated.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following according to the timetables in your June 25, 2009, submission:

1. An assessment of spontaneous reports of lung toxicity associated with Multaq (dronedarone hydrochloride). Following approval, and according to the following timetable, submit a yearly report (containing both interval-based and comprehensive data) analyzing spontaneous adverse event reports received that describe lung toxicity. Specialized follow-up (using forms included in your June 4, 2008, submission) should be obtained on these cases to collect additional information on the event (e.g., symptoms, medical history, concomitant medications, laboratory evaluations, imaging results, biopsy results).

Interim Report Submissions:	September 2010
	September 2011
	September 2012
	September 2013
	September 2014
Final Report Submission:	September 2016

2. Conduct an epidemiologic study using claims or electronic health records data to evaluate the potential association between Multaq (dronedarone hydrochloride) use and lung toxicities. Following approval and according to the following timeline, submit a yearly report (containing both interval-based and comprehensive data) on the incidence rate of lung toxicity in Multaq (dronedarone hydrochloride) users vs. non-Multaq (dronedarone hydrochloride) users.

Submission of Final Study Plan:	September 2009
Interim Report Submissions:	December 2010
	December 2011
	December 2012
	December 2013
	December 2014
Final Report Submission:	December 2016

3. Conduct an epidemiologic study using claims or electronic health records data to evaluate the potential association between Multaq (dronedarone hydrochloride) use and neuropathies (including optic neuropathy). Following approval and according to the following timeline, submit a yearly report (containing both interval-based and comprehensive data) on the incidence rate of neuropathies in Multaq (dronedarone hydrochloride) users vs. non-Multaq (dronedarone hydrochloride) users.

Submission of Final Study Plan:	September 2009
Interim Report Submissions:	December 2010
	December 2011
	December 2012
	December 2013
	December 2014
Final Report Submission:	December 2016

4. Conduct an epidemiologic study using claims or electronic health records data to evaluate the potential association between Multaq (dronedarone hydrochloride) use and severe skin reactions. Following approval and according to the following timeline, submit a yearly report (containing both interval-based and comprehensive data) on the incidence rate of severe skin reactions in Multaq (dronedarone hydrochloride) users vs. non-Multaq (dronedarone hydrochloride) users.

Submission of Final Study Plan:	September 2009
Interim Report Submissions:	December 2010
	December 2011
	December 2012
	December 2013
	December 2014
Final Report Submission:	December 2016

5. Conduct an epidemiologic study using claims or electronic health records data to evaluate the use of Multaq (dronedarone hydrochloride) in patients for whom its use is contraindicated. Following approval and according to the following timeline, submit a yearly report (containing both interval-based and comprehensive data) to determine the

extent of dronedarone use in patients for whom its use is contraindicated (for example, patients who have been hospitalized for decompensated heart failure in the 30 days preceding dronedarone initiation).

Submission of Final Study Plan:	September 2009
Interim Report Submissions:	December 2010
	December 2011
	December 2012
	December 2013
	December 2014
Final Report Submission:	December 2016

In your June 25, 2009, submission you agreed that will conduct these 5 studies according to the above timetables.

Submit the protocols to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Your proposed REMS, submitted on June 10, 2009, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

1. Periodic surveys of healthcare professionals to monitor the effectiveness of the interventions in educating prescribers on the goals of the REMS and to monitor appropriate prescribing of Multaq (dronedarone hydrochloride)

2. Periodic surveys of patients to monitor the effectiveness of the interventions in educating patients on the safe and appropriate use of Multaq (dronedarone hydrochloride)

3. A postmarketing epidemiologic study of Multaq (dronedarone hydrochloride) will be conducted in a claims database to assess drug utilization by inappropriate patient (contraindicated) population.

4. Patients' understanding of the serious risks of Multaq (dronedarone hydrochloride)

5. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

6. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

You should submit the final methodology and content of the patient survey at least 90 days prior to initiation of the survey.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify the amendment containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22-425 - REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 22-425
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 22-425
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please contact Russell Fortney, Regulatory Project Manager at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures: Agreed-upon labeling and REMS

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MULTAQ safely and effectively. See full prescribing information for MULTAQ.

MULTAQ (dronedarone) Tablets
Initial U.S. Approval: 2009

WARNING: HEART FAILURE

MULTAQ is contraindicated in patients with NYHA Class IV heart failure or NYHA Class II - III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic (4).

In a placebo-controlled study in patients with severe heart failure requiring recent hospitalization or referral to a specialized heart failure clinic for worsening symptoms (the ANDROMEDA Study), patients given dronedarone had a greater than two-fold increase in mortality. Such patients should not be given dronedarone (14.3).

INDICATIONS AND USAGE

MULTAQ is an antiarrhythmic drug indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors (i.e., age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥50 mm or left ventricular ejection fraction [LVEF] <40%), who are in sinus rhythm or who will be cardioverted (1, 14).

DOSAGE AND ADMINISTRATION

One tablet of 400 mg twice a day with morning and evening meals (2)

DOSAGE FORMS AND STRENGTHS

400 mg film-coated tablets (3)

CONTRAINDICATIONS

- Class IV heart failure or symptomatic heart failure with a recent decompensation (Boxed Warning, 4)
- Second- or third- degree atrioventicular (AV) block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker) (4)
- Bradycardia <50 bpm (4)
- Concomitant use of a strong CYP3A inhibitor (4)
- Concomitant use of drugs or herbal products that prolong the QT interval and may induce Torsade de Pointes (4)
- QTc Bazett interval ≥500 ms (4)
- Severe hepatic impairment (4)
- Pregnancy (4, 8.1)
- Nursing mothers (4, 8.3)

WARNINGS AND PRECAUTIONS

- Heart failure: If heart failure develops or worsens, consider the suspension or discontinuation of MULTAQ (5.1)
- Hypokalemia and hypomagnesemia: Maintain potassium and magnesium levels within the normal range (5.2)
- QT prolongation: Stop MULTAQ if QTc Bazett ≥500ms (5.3)
- Increase in creatinine: Within a week, MULTAQ causes a small increase in serum creatinine that does not reflect a change in underlying renal function (5.4)
- Teratogen: Women of childbearing potential should use effective contraception while using MULTAQ (5.5)

ADVERSE REACTIONS

Most common adverse reactions (≥2%) are diarrhea, nausea, abdominal pain, vomiting, and asthenia (6)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Dronedarone is metabolized by CYP 3A and is a moderate inhibitor of CYP 3A and CYP 2D6 and has potentially important pharmacodynamic interactions (7)

- Antiarrhythmics: Avoid concomitant use (4, 7.1)
- Digoxin: Consider discontinuation or halve dose of digoxin before treatment and monitor (7.1, 7.3)
- Calcium channel blockers (CCB): Initiate CCB with low dose and increase after ECG verification of tolerability (7.1,7.2, 7.3)
- Beta-blockers: May provoke excessive bradycardia, Initiate with low dose and increase after ECG verification of tolerability (7.1, 7.3)
- CYP 3A inducers: Avoid concomitant use (7.2)
- Grapefruit juice: Avoid concomitant use (7.2)
- Statins: Follow label recommendations for concomitant use of certain statins with a CYP 3A and P-gP inhibitor like dronedarone (7.3)
- CYP 3A substrates with a narrow therapeutic index (e.g., sirolimus and tacrolimus): Monitor and adjust dosage of concomitant drug as needed when used with MULTAQ (7.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 7/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: HEART FAILURE

MULTAQ is contraindicated in patients with NYHA Class IV heart failure, or NYHA Class II - III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic *[see Contraindications (4)]*.

In a placebo-controlled study in patients with severe heart failure requiring recent hospitalization or referral to a specialized heart failure clinic for worsening symptoms (the ANDROMEDA Study), patients given dronedarone had a greater than two-fold increase in mortality. Such patients should not be given dronedarone *[see Clinical Studies (14.3)]*.

1 INDICATIONS AND USAGE

MULTAQ® is indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors (i.e., age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥50 mm or left ventricular ejection fraction [LVEF] <40%), who are in sinus rhythm or who will be cardioverted *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

The only recommended dosage of MULTAQ is 400 mg twice daily in adults. MULTAQ should be taken as one tablet with the morning meal and one tablet with the evening meal.

Treatment with Class I or III antiarrhythmics (e.g., amiodarone, flecainide, propafenone, quinidine, disopyramide, dofetilide, sotalol) or drugs that are strong inhibitors of CYP3A (e.g., ketoconazole) must be stopped before starting MULTAQ *[see Contraindications (4)]*.

3 DOSAGE FORMS AND STRENGTHS

MULTAQ 400 mg tablets are provided as white film-coated tablets for oral administration, oblong-shaped, engraved with a double wave marking on one side and "4142" code on the other side.

4 CONTRAINDICATIONS

MULTAQ is contraindicated in patients with:

- NYHA Class IV heart failure or NYHA Class II - III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic *[see Boxed Warning and Clinical Studies (14.3)]*
- Second- or third-degree atrioventricular (AV) block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker)
- Bradycardia <50 bpm

- Concomitant use of strong CYP 3A inhibitors, such as ketoconazole, itraconazole, voriconazole, cyclosporine, telithromycin, clarithromycin, nefazodone, and ritonavir *[see Drug Interactions (7.2)]*
- Concomitant use of drugs or herbal products that prolong the QT interval and might increase the risk of Torsade de Pointes, such as phenothiazine anti-psychotics, tricyclic antidepressants, certain oral macrolide antibiotics, and Class I and III antiarrhythmics
- QTc Bazett interval ≥500 ms or PR interval >280 ms
- Severe hepatic impairment
- Pregnancy (Category X): MULTAQ may cause fetal harm when administered to a pregnant woman. MULTAQ is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.
- Nursing mothers *[see Use in Specific Populations (8.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Patients with New or Worsening Heart Failure during Treatment

Advise patients to consult a physician if they develop signs or symptoms of heart failure, such as weight gain, dependent edema, or increasing shortness of breath. There are limited data available for AF/AFL patients who develop worsening heart failure during treatment with MULTAQ. If heart failure develops or worsens, consider the suspension or discontinuation of MULTAQ.

5.2 Hypokalemia and Hypomagnesemia with Potassium-Depleting Diuretics

Hypokalemia or hypomagnesemia may occur with concomitant administration of potassium-depleting diuretics. Potassium levels should be within the normal range prior to administration of MULTAQ and maintained in the normal range during administration of MULTAQ.

5.3 QT Interval Prolongation

Dronedarone induces a moderate (average of about 10 ms but much greater effects have been observed) QTc (Bazett) prolongation *[see Clinical Pharmacology (12.2) and Clinical Studies (14.1)]*. If the QTc Bazett interval is ≥500 ms, MULTAQ should be stopped *[see Contraindications (4)]*.

5.4 Increase in Creatinine after Treatment Initiation

Serum creatinine levels increase by about 0.1 mg/dL following dronedarone treatment initiation. The elevation has a rapid onset, reaches a plateau after 7 days and is reversible after discontinuation. If an increase in serum creatinine occurs and plateaus, this increased value should be used as the patient's new baseline. The change in creatinine levels has been shown to be the result of an inhibition of creatinine's tubular secretion, with no effect upon the glomerular filtration rate.

5.5 Women of Childbearing Potential

Premenopausal women who have not undergone a hysterectomy or oophorectomy must use effective contraception while using MULTAQ. Dronedarone caused fetal harm in animal studies

at doses equivalent to recommended human doses. Women of childbearing potential should be counseled regarding appropriate contraceptive choices taking into consideration their underlying medical conditions and lifestyle preferences *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following safety concerns are described elsewhere in the label:

- New or worsening heart failure *[see Warnings and Precautions (5.1)]*
- Hypokalemia and hypomagnesemia with potassium-depleting diuretics *[see Warnings and Precautions (5.2)]*
- QT prolongation *[see Warnings and Precautions (5.3)]*

The safety evaluation of dronedarone 400 mg twice daily in patients with AF or AFL is based on 5 placebo controlled studies, ATHENA, EURIDIS, ADONIS, ERATO and DAFNE. In these studies, a total of 6285 patients were randomized and treated, 3282 patients with MULTAQ 400 mg twice daily, and 2875 with placebo. The mean exposure across studies was 12 months. In ATHENA, the maximum follow-up was 30 months.

In clinical trials, premature discontinuation because of adverse reactions occurred in 11.8% of the dronedarone-treated patients and in 7.7% of the placebo-treated group. The most common reasons for discontinuation of therapy with MULTAQ were gastrointestinal disorders (3.2 % versus 1.8% in the placebo group) and QT prolongation (1.5% versus 0.5% in the placebo group).

The most frequent adverse reactions observed with MULTAQ 400 mg twice daily in the 5 studies were diarrhea, nausea, abdominal pain, vomiting, and asthenia.

Table 1 displays adverse reactions more common with dronedarone 400 mg twice daily than with placebo in AF or AFL patients, presented by system organ class and by decreasing order of frequency. Adverse laboratory and ECG effects are presented separately in Table 2.

Table 1: Adverse Drug Reactions that Occurred in at Least 1% of Patients and Were More Frequent than Placebo

	Placebo (N=2875)	Dronedarone 400 mg twice daily (N=3282)
Gastrointestinal		
Diarrhea	6%	9%
Nausea	3%	5%
Abdominal pain	3%	4%
Vomiting	1%	2%
Dyspeptic signs and symptoms	1%	2%
General		
Asthenic conditions	5%	7%
Cardiac		
Bradycardia	1%	3%
Skin and subcutaneous tissue		
Including rashes (generalized, macular, maculo-papular, erythematous), pruritus, eczema, dermatitis, dermatitis allergic	3%	5%

Photosensitivity reaction and dysgeusia have also been reported at an incidence less than 1% in patients treated with MULTAQ.

The following laboratory data/ECG parameters were reported with MULTAQ 400 mg twice daily.

Table 2: Laboratory data/ECG parameters not necessarily reported as adverse events

	Placebo	MULTAQ 400 mg twice daily
	(N=2875)	(N=3282)
Serum creatinine increased ≥10% five days after treatment initiation	21%	51%
	(N=2237)	(N=2701)
QTc Bazett prolonged (>450 ms in males >470 ms in females)	19%	28%

Assessment of demographic factors such as gender or age on the incidence of treatment-emergent adverse events did not suggest an excess of adverse events in any particular sub-group.

7 DRUG INTERACTIONS

Dronedarone is metabolized primarily by CYP 3A and is a moderate inhibitor of CYP 3A and CYP 2D6 *[see Clinical Pharmacology (12.3)]*. Dronedarone's blood levels can therefore be affected by inhibitors and inducers of CYP 3A, and dronedarone can interact with drugs that are substrates of CYP 3A and CYP 2D6.

Dronedarone has no significant potential to inhibit CYP 1A2, CYP 2C9, CYP 2C19, CYP 2C8 and CYP 2B6. It has the potential to inhibit P-glycoprotein (P-gP) transport.
Pharmacodynamic interactions can be expected with beta-blockers; calcium antagonists and digoxin *[see Drug Interactions (7.1)]*.

In clinical trials, patients treated with dronedarone received concomitant medications including beta-blockers, digoxin, calcium antagonists (including those with heart rate-lowering effects), statins and oral anticoagulants.

7.1 Pharmacodynamic Interactions

Drugs prolonging the QT interval (inducing Torsade de Pointes)

Co-administration of drugs prolonging the QT interval (such as certain phenothiazines, tricyclic antidepressants, certain macrolide antibiotics, and Class I and III antiarrhythmics) is contraindicated because of the potential risk of Torsade de Pointes-type ventricular tachycardia *[see Contraindications (4)]*.

Digoxin

Digoxin can potentiate the electrophysiologic effects of dronedarone (such as decreased AV-node conduction). In clinical trials, increased levels of digoxin were observed when dronedarone was co-administered with digoxin. Gastrointestinal disorders were also increased.
Because of the pharmacokinetic interaction *[see Drug Interaction (7.3)]* and possible pharmacodynamic interaction, reconsider the need for digoxin therapy. If digoxin treatment is continued, halve the dose of digoxin, monitor serum levels closely, and observe for toxicity.

Calcium channel blockers

Calcium channel blockers with depressant effects on the sinus and AV nodes could potentiate dronedarone's effects on conduction.

Give low doses of calcium channel blockers initially and increase only after ECG verification of good tolerability *[see Drug Interactions (7.3)]*.

Beta-blockers

In clinical trials, bradycardia was more frequently observed when dronedarone was given in combination with beta-blockers.

Give low dose of beta-blockers initially, and increase only after ECG verification of good tolerability *[see Drug Interactions (7.3)]*.

7.2 Effects of Other Drugs on Dronedarone

Ketoconazole and other potent CYP 3A inhibitors

Repeated doses of ketoconazole, a strong CYP 3A inhibitor, resulted in a 17-fold increase in dronedarone exposure and a 9-fold increase in C_{max}. Concomitant use of ketoconazole as well as other potent CYP 3A inhibitors such as itraconazole, voriconazole, ritonavir, clarithromycin, and nefazodone is contraindicated *[see Contraindications (4)]*.

Grapefruit juice

Grapefruit juice, a moderate inhibitor of CYP 3A, resulted in a 3-fold increase in dronedarone exposure and a 2.5-fold increase in C_{max}. Therefore, patients should avoid grapefruit juice beverages while taking MULTAQ.

Rifampin and other CYP 3A inducers

Rifampin decreased dronedarone exposure by 80%. Avoid rifampin or other CYP 3A inducers such as phenobarbital, carbamazepine, phenytoin, and St John's wort with dronedarone because they decrease its exposure significantly.

Calcium channel blockers

Verapamil and diltiazem are moderate CYP 3A inhibitors and increase dronedarone exposure by approximately 1.4-to 1.7-fold *[see Drug Interactions (7.1, 7.3)]*.

Pantoprazole

Pantoprazole, a drug that increases gastric pH, did not have a significant effect on dronedarone pharmacokinetics.

7.3 Effects of Dronedarone on Other Drugs

Statins

Dronedarone increased simvastatin/simvastatin acid exposure by 4- and 2-fold, respectively. Because of multiple mechanisms of interaction with statins (CYPs and transporters), follow statin label recommendations for use with CYP 3A and P-gP inhibitors such as dronedarone.

Calcium channel blockers

Dronedarone increases calcium channel blocker (verapamil, diltiazem or nifedipine) exposure by 1.4- to 1.5-fold *[see Drug Interactions (7.1)]*.

Sirolimus, tacrolimus, and other CYP3A substrates with narrow therapeutic range

Dronedarone can increase plasma concentrations of tacrolimus, sirolimus, and other CYP 3A substrates with a narrow therapeutic range when given orally. Monitor plasma concentrations and adjust dosage appropriately.

Beta-blockers and other CYP 2D6 substrates

Dronedarone increased propranolol exposure by approximately 1.3-fold following single dose administration. Dronedarone increased metoprolol exposure by 1.6-fold following multiple dose administration *[see Drug Interaction (7.1)]*. Other CYP 2D6 substrates, including other beta-

blockers, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs) may have increased exposure upon co-administration with dronedarone.

Digoxin and P-glycoprotein substrates

Dronedarone increased digoxin exposure by 2.5-fold by inhibiting the P-gP transporter *[see Drug Interactions (7.1)]*. Other P-gP substrates are expected to have increased exposure when coadministered with dronedarone.

Warfarin and losartan (CYP 2C9 substrates)

In healthy subjects, dronedarone at a dose of 600 mg twice daily increased S-warfarin exposure by 1.2-fold with no change in R-warfarin and with no clinically significant increase in INR. In clinical trials in patients with AF/AFL, there was no observed excess risk of bleeding compared to placebo when dronedarone was co-administered with oral anticoagulants. Monitor INR per the warfarin label.

No interaction was observed between dronedarone and losartan.

Theophylline (CYP 1A2 substrate)

Dronedarone does not increase steady state theophylline exposure.

Oral contraceptives

No decreases in ethinylestradiol and levonorgestrel concentrations were observed in healthy subjects receiving dronedarone concomitantly with oral contraceptives.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4)]*

MULTAQ may cause fetal harm when administered to a pregnant woman. In animal studies, dronedarone was teratogenic in rats at the maximum recommended human dose (MRHD), and in rabbits at half the MRHD. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

When pregnant rats received dronedarone at oral doses greater than or equal to the MRHD (on a mg/m^2 basis), fetuses had increased rates of external, visceral and skeletal malformations (cranioschisis, cleft palate, incomplete evagination of pineal body, brachygnathia, partially fused carotid arteries, truncus arteriosus, abnormal lobation of the liver, partially duplicated inferior vena cava, brachydactyly, ectrodactylia, syndactylia, and anterior and/or posterior club feet). When pregnant rabbits received dronedarone, at a dose approximately half the MRHD (on a mg/m^2 basis), fetuses had an increased rate of skeletal abnormalities (anomalous ribcage and vertebrae, pelvic asymmetry) at doses ≥20 mg/kg (the lowest dose tested and approximately half the MRHD on a mg/m^2 basis).

Actual animal doses: rat (≥80 mg/kg/day); rabbit (≥20 mg/kg)

8.3 Nursing Mothers
It is not known whether MULTAQ is excreted in human milk. Dronedarone and its metabolites are excreted in rat milk. During a pre- and post-natal study in rats, maternal dronedarone administration was associated with minor reduced body-weight gain in the offspring. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MULTAQ, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother *[see Contraindications (4)]*.

8.4 Pediatric Use
Safety and efficacy in children below the age of 18 years have not been established.

8.5 Geriatric Use
More than 4500 patients with AF or AFL aged 65 years or above were included in the MULTAQ clinical program (of whom more than 2000 patients were 75 years or older). Efficacy and safety were similar in elderly and younger patients.

8.6 Renal Impairment
Patients with renal impairment were included in clinical studies. Because renal excretion of dronedarone is minimal *[see Clinical Pharmacology (12.3)]*, no dosing alteration is needed.

8.7 Hepatic Impairment
Dronedarone is extensively metabolized by the liver. There is little clinical experience with moderate hepatic impairment and none with severe impairment. No dosage adjustment is recommended for moderate hepatic impairment *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

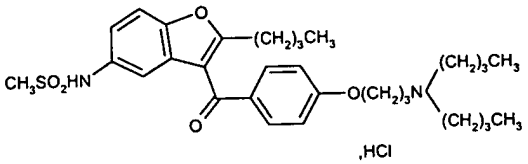
10 OVERDOSAGE

In the event of overdosage, monitor the patient's cardiac rhythm and blood pressure. Treatment should be supportive and based on symptoms.

It is not known whether dronedarone or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis or hemofiltration). There is no specific antidote available.

11 DESCRIPTION

Dronedarone HCl is a benzofuran derivative with the following chemical name:
N-{2-butyl-3-[4-(3-dibutylaminopropoxy)benzoyl]benzofuran-5-yl} methanesulfonamide, hydrochloride.
Dronedarone HCl is a white fine powder that is practically insoluble in water and freely soluble in methylene chloride and methanol.
Its empirical formula is $C_{31}H_{44}N_2O_5S$, HCl with a relative molecular mass of 593.2. Its structural formula is:



MULTAQ is provided as tablets for oral administration.

Each tablet of MULTAQ contains 400 mg of dronedarone (expressed as base).

The inactive ingredients are:

Core of the tablets- hypromellose, starch, crospovidone, poloxamer 407, lactose monohydrate, colloidal silicon dioxide, magnesium stearate.

Coating / polishing of the tablets- hypromellose, polyethylene glycol 6000, titanium dioxide, carnauba wax.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of dronedarone is unknown. Dronedarone has antiarrhythmic properties belonging to all four Vaughan-Williams classes, but the contribution of each of these activities to the clinical effect is unknown.

12.2 Pharmacodynamics

Electrophysiological effects

Dronedarone exhibits properties of all four Vaughn-Williams antiarrhythmic classes, although it is unclear which of these are important in producing dronedarone's clinical effects. The effect of dronedarone on 12-lead ECG parameters (heart rate, PR, and QTc) was investigated in healthy subjects following repeated oral doses up to 1600 mg once daily or 800 mg twice daily for 14 days and 1600 mg twice daily for 10 days. In the dronedarone 400 mg twice daily group, there was no apparent effect on heart rate; a moderate heart rate lowering effect (about 4 bpm) was noted at 800 mg twice daily. There was a clear dose-dependent effect on PR-interval with an increase of +5 ms at 400 mg twice daily and up to +50 ms at 1600 mg twice daily. There was a moderate dose related effect on the QTc-interval with an increase of +10 ms at 400 mg twice daily and up to +25 ms with 1600 mg twice daily.

DAFNE study

DAFNE was a dose-response study in patients with recurrent AF, evaluating the effect of dronedarone in comparison with placebo in maintaining sinus rhythm. The doses of dronedarone in this study were 400, 600 and 800 mg twice a day. In this small study, doses above 400 mg were not more effective and were less well tolerated.

12.3 Pharmacokinetics

Dronedarone is extensively metabolized and has low systemic bioavailability; its bioavailability is increased by meals. Its elimination half life is 13-19 hours.

Absorption

Because of presystemic first pass metabolism the absolute bioavailability of dronedarone without food is low, about 4%. It increases to approximately 15% when dronedarone is administered with a high fat meal. After oral administration in fed conditions, peak plasma concentrations of dronedarone and the main circulating active metabolite (N-debutyl metabolite) are reached within 3 to 6 hours. After repeated administration of 400 mg twice daily, steady state is reached within 4 to 8 days of treatment and the mean accumulation ratio for dronedarone ranges from 2.6 to 4.5. The steady state C_{max} and exposure of the main N-debutyl metabolite is similar to that of the parent compound. The pharmacokinetics of dronedarone and its N-debutyl metabolite both deviate moderately from dose proportionality: a 2-fold increase in dose results in an approximate 2.5- to 3.0- fold increase with respect to C_{max} and AUC.

Distribution

The *in vitro* plasma protein binding of dronedarone and its N-debutyl metabolite is >98 % and not saturable. Both compounds bind mainly to albumin. After intravenous (IV) administration the volume of distribution at steady state is about 1400 L.

Metabolism

Dronedarone is extensively metabolized, mainly by CYP 3A. The initial metabolic pathway includes N-debutylation to form the active N-debutyl metabolite, oxidative deamination to form the inactive propanoic acid metabolite, and direct oxidation. The metabolites undergo further metabolism to yield over 30 uncharacterized metabolites. The N-debutyl metabolite exhibits pharmacodynamic activity but is 1/10 to 1/3 as potent as dronedarone

Excretion/Elimination

In a mass balance study with orally administered dronedarone (^{14}C-labeled) approximately 6% of the labeled dose was excreted in urine, mainly as metabolites (no unchanged compound excreted in urine), and 84% was excreted in feces, mainly as metabolites. Dronedarone and its N-debutyl active metabolite accounted for less than 15% of the resultant radioactivity in the plasma.

After IV administration the plasma clearance of dronedarone ranges from 130 to 150 L/h. The elimination half-life of dronedarone ranges from 13 to 19 hours.

Special populations

Gender

Dronedarone exposures are on average 30% higher in females than in males.

Race

Pharmacokinetic differences related to race were not formally assessed. However, based on a cross study comparison, following single dose administration (400 mg), Asian males (Japanese) have about a 2-fold higher exposure than Caucasian males. The pharmacokinetics of dronedarone in other races has not been assessed.

Elderly
Of the total number of subjects in clinical studies of dronedarone, 73% were 65 years of age and over and 34% were 75 and over. In patients aged 65 years old and above, dronedarone exposures are 23% higher than in patients less than 65 years old *[see Use in Specific Populations (8.5)]*.

Hepatic impairment
In subjects with moderate hepatic impairment, the mean dronedarone exposure increased by 1.3-fold relative to subjects with normal hepatic function and the mean exposure of the N-debutyl metabolite decreased by about 50%. Pharmacokinetic data were significantly more variable in subjects with moderate hepatic impairment.

The effect of severe hepatic impairment on the pharmacokinetics of dronedarone was not assessed *[see Contraindications (4)]*.

Renal impairment
Consistent with the low renal excretion of dronedarone, no pharmacokinetic difference was observed in subjects with mild or moderate renal impairment compared to subjects with normal renal function *[see Use in Specific Populations (8.6)]*. No pharmacokinetic difference was observed in patients with mild to severe renal impairment in comparison with patients with normal renal function.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
In studies in which dronedarone was administered to rats and mice for up to 2 years at doses of up to 70 mg/kg/day and 300 mg/kg/day, respectively, there was an increased incidence of histiocytic sarcomas in dronedarone-treated male mice (300 mg/kg/day or 5X the maximum recommended human dose based on AUC comparisons), mammary adenocarcinomas in dronedarone-treated female mice (300 mg/kg/day or 8X MRHD based on AUC comparisons) and hemangiomas in dronedarone-treated male rats (70 mg/kg/day or 5X MRHD based on AUC comparisons).

Dronedarone did not demonstrate genotoxic potential in the in vivo mouse micronucleus test, the Ames bacterial mutation assay, the unscheduled DNA synthesis assay, or an in vitro chromosomal aberration assay in human lymphocytes. S-9 processed dronedarone, however, was positive in a V79 transfected Chinese hamster V79 assay.

In fertility studies conducted with female rats, dronedarone given prior to breeding and implantation caused an increase in irregular estrus cycles and cessation of cycling at doses $\geq$10mg/kg (equivalent to 0.12X the MRHD on a mg/m^2 basis).

Corpora lutea, implantations and live fetuses were decreased at 100 mg/kg (equivalent to 1.2X the MRHD on a mg/m^2 basis). There were no reported effects on mating behavior or fertility of male rats at doses of up to 100 mg/kg/day.

13.3 Developmental Toxicity

Dronedarone was teratogenic in rats given oral doses ≥80 mg/kg/day (a dose equivalent to the maximum recommended human dose [MHRD] on a mg/m^2 basis), with fetuses showing external, visceral and skeletal malformations (cranioschisis, cleft palate, incomplete evagination of pineal body, brachygnathia, partially fused carotid arteries, truncus arteriosus, abnormal lobation of the liver, partially duplicated inferior vena cava, brachydactyly, ectrodactylia, syndactylia, and anterior and/or posterior club feet). In rabbits, dronedarone caused an increase in skeletal abnormalities (anomalous ribcage and vertebrae, pelvic asymmetry) at doses ≥20 mg/kg (the lowest dose tested and approximately half the MRHD on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 ATHENA Study

ATHENA was a multicenter, multinational, double blind, and randomized placebo-controlled study of dronedarone in 4628 patients with a recent history of AF/AFL who were in sinus rhythm or who were to be converted to sinus rhythm. The objective of the study was to determine whether dronedarone could delay death from any cause or hospitalization for cardiovascular reasons.

Initially patients were to be ≥70 years old, or <70 years old with at least one risk factor (including hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥50 mm or LVEF<0.40). The inclusion criteria were later changed such that patients were to be ≥75 years old, or ≥70 years old with at least one risk factor. Patients had to have both AF/AFL and sinus rhythm documented within the previous 6 months. Patients could have been in AF/AFL or in sinus rhythm at the time of randomization, but patients not in sinus rhythm were expected to be either electrically or chemically converted to normal sinus rhythm after anticoagulation.

Subjects were randomized and treated for up to 30 months (median follow-up: 22 months) with either MULTAQ 400 mg twice daily (2301 patients) or placebo (2327 patients), in addition to conventional therapy for cardiovascular diseases that included beta-blockers (71%), ACE inhibitors or angiotensin II receptor blockers (ARBs)(69%), digoxin (14%), calcium antagonists (14%), statins (39%), oral anticoagulants (60%), aspirin (44%), other chronic antiplatelet therapy (6%) and diuretics (54%).

The primary endpoint of the study was the time to first hospitalization for cardiovascular reasons or death from any cause. Time to death from any cause, time to first hospitalization for cardiovascular reasons, and time to cardiovascular death and time to all causes of death were also explored.

Patients ranged in age from 23 to 97 years; 42% were 75 years old or older. Forty-seven percent (47%) of patients were female and a majority was Caucasian (89%). Approximately seventy percent (71%) of those enrolled had no history of heart failure. The median ejection fraction was 60%. Twenty-nine percent (29%) of patients had heart failure, mostly NYHA class II (17%) The majority had hypertension (86%) and structural heart disease (60%).

Results are shown in Table 3. MULTAQ reduced the combined endpoint of cardiovascular hospitalization or death from any cause by 24.2% when compared to placebo. This difference was entirely attributable to its effect on cardiovascular hospitalization, principally hospitalization related to AF.

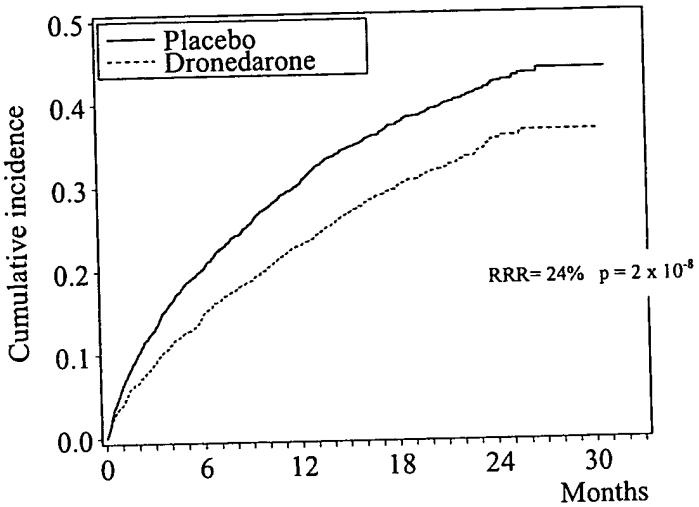
Other endpoints, death from any cause and first hospitalization for cardiovascular reasons, are shown in Table 3. Secondary endpoints count all first events of a particular type, whether or not they were preceded by a different type of event.

Table 3: Incidence of Endpoint Events

	Placebo (N= 2327)	**MULTAQ 400mg BID (N= 2301)**	**HR**	**95% CI**	**p-Value**
Primary endpoint					
Cardiovascular hospitalization or death from any cause	913 (39.2%)	727 (31.6%)	0.76	[0.68 - 0.83]	<0.0001
Components of the endpoint (as first event)					
• Cardiovascular hospitalization	856 (36.8%)	669 (29.1%)			
• Death from any cause	57 (2.4%)	58 (2.5%)			
Secondary endpoints (any time in study)					
Death from any cause	135 (5.8%)	115 (5.0%)	0.86	[0.67 - 1.11]	0.24
Cardiovascular hospitalization	856 (36.8%)	669 (29.1%)	0.74	[0.67 - 0.82]	<0.0001
Components of the cardiovascular hospitalization endpoint (as first event)					
• AF and other supraventricular rhythm disorders	456 (19.6%)	292 (12.7%)	0.61	[0.53 - 0.71]	<0.0001
• Other	400 (17.2%)	377 (16.4%)	0.89	[0.77 - 1.03]	0.11

The Kaplan-Meier cumulative incidence curves showing the time to first event are displayed in Figure 1. The event curves separated early and continued to diverge over the 30 month follow-up period.

Figure 1: Kaplan-Meier Cumulative Incidence Curves from Randomization to First Cardiovascular Hospitalization or Death from any Cause



Number at risk:

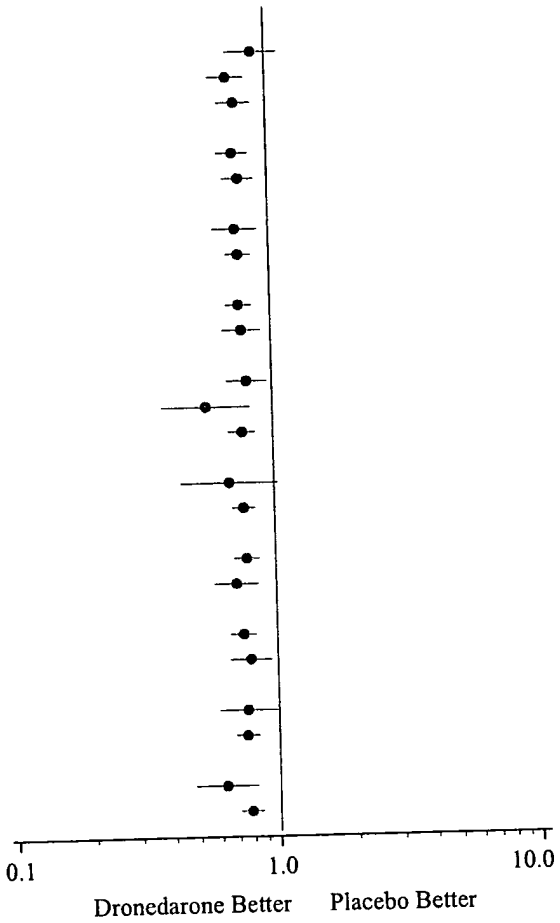
Placebo	2327	1858	1625	1072	385	3
Dronedarone	2301	1963	1776	1177	403	2

Reasons for hospitalization included major bleeding (1% in both groups), syncope (1% in both groups), and ventricular arrhythmia (<1% in both groups).

The reduction in cardiovascular hospitalization or death from any cause was generally consistent in all subgroups based on baseline characteristics or medications (ACE inhibitors or ARBs; beta-blockers, digoxin, statins, calcium channel blockers, diuretics) (see Figure 2).

Figure 2: Relative Risk (MULTAQ versus placebo) Estimates with 95% Confidence Intervals According to Selected Baseline Characteristics: First Cardiovascular Hospitalization or Death from any Cause.

Characteristic	N	RR [95% CI] (a)	P-value (b)
Age (years)			
<65	873	0.89 [0.71;1.11]	
[65-75[	1830	0.71 [0.60;0.83]	
>=75	1925	0.75 [0.65;0.87]	0.27
Gender			
Male	2459	0.74 [0.64;0.85]	
Female	2169	0.77 [0.67;0.89]	0.65
Presence of AF/AFL			
Yes	1155	0.74 [0.61;0.91]	
No	3473	0.76 [0.68;0.85]	0.85
Structural Heart Disease			
Yes	2732	0.76 [0.67;0.85]	
No	1853	0.77 [0.65;0.92]	0.85
NYHA			
Class I or II	1165	0.80 [0.67;0.96]	
Class III	200	0.56 [0.38;0.82]	
No CHF	3263	0.76 [0.68;0.86]	0.22
LVEF(%)			
<35	179	0.68 [0.44;1.03]	
>=35	4365	0.76 [0.69;0.84]	0.58
Beta blocking agents			
Yes	3269	0.78 [0.69;0.87]	
No	1359	0.71 [0.58;0.86]	0.41
ACE inhibitors or ARBs			
Yes	3216	0.74 [0.66;0.83]	
No	1412	0.79 [0.66;0.95]	0.59
Digitalis			
Yes	629	0.76 [0.59;0.98]	
No	3999	0.76 [0.68;0.84]	0.96
Calcium antagonists (c)			
Yes	638	0.63 [0.48;0.82]	
No	3990	0.78 [0.70;0.87]	0.15



a Determined from Cox regression model
b P-value of interaction between baseline characteristics and treatment based on Cox regression model
c Calcium antagonists with heart rate lowering effects restricted to diltiazem, verapamil and bepridil

14.2 EURIDIS and ADONIS Studies

In EURIDIS and ADONIS, a total of 1237 patients in sinus rhythm with a prior episode of AF or AFL were randomized in an outpatient setting and treated with either MULTAQ 400 mg twice daily (n=828) or placebo (n=409) on top of conventional therapies (including oral anticoagulants, beta-blockers, ACE inhibitors or ARBs, chronic antiplatelet agents, diuretics, statins, digoxin, and calcium channel blockers). Patients had at least one ECG-documented AF/AFL episode during the 3 months prior to study entry but were in sinus rhythm for at least one hour. Patients ranged in age from 20 to 88 years, with the majority being Caucasian (97%), male (70%) patients. The most common co-morbidities were hypertension (56.8%) and structural heart disease (41.5%), including coronary heart disease (21.8%). Patients were followed for 12 months.

In the pooled data from EURIDIS and ADONIS as well as in the individual trials, dronedarone delayed the time to first recurrence of AF/AFL (primary endpoint), lowering the risk of first AF/AFL recurrence during the 12-month study period by about 25%,with an absolute difference in recurrence rate of about 11% at 12 months.

14.3 ANDROMEDA Study (Increased Mortality in Patients with Severe Heart Failure)

Patients recently hospitalized with symptomatic heart failure and severe left ventricular systolic dysfunction (wall motion index ≤1.2) were randomized to either MULTAQ 400 mg twice daily or matching placebo, with a primary composite end point of all-cause mortality or hospitalization for heart failure. After enrollment of 627 of 1000 planned patients (310 and 317 in the dronedarone and placebo groups, respectively), and a median follow-up of 63 days, the trial was terminated because of excess mortality in the dronedarone group. Twenty-five (25) patients in the dronedarone group (8.1%) versus 12 patients in the placebo group (3.8%) had died, hazard ratio 2.13; 95% CI: 1.07 to 4.25; p=0.027. The main reason for death was worsening heart failure. There were also excess hospitalizations for cardiovascular reasons in the dronedarone group (71 versus 51 for placebo) *[see Boxed Warning and Contraindications (4)]*.

The populations enrolled in the ANDROMEDA and ATHENA studies were significantly different. The patients enrolled in ANDROMEDA had relatively severe heart failure and had been hospitalized, or referred to a specialty heart failure clinic, for worsening symptoms of heart failure, notably shortness of breath. Note that these patients may have been clinically improved at the time of enrollment and it is the history of decompensation that characterized them. Patients enrolled into ANDROMEDA were predominantly NYHA Class II (40%) and III (57%), and only 38% had a history of AF/AFL (25% had AF at randomization). In contrast, in ATHENA, 71% of patients had no heart failure, 25% were NYHA Class I or II, and only 4% were Class III. All patients had a history of AF/AFL.

16 HOW SUPPLIED/STORAGE AND HANDLING

MULTAQ 400-mg tablets are provided as white film-coated tablets for oral administration, oblong-shaped, engraved with a double wave marking on one side and "4142" code on the other side in:

Bottles of 60 tablets, NDC 0024-4142-60
Bottles of 180 tablets, NDC 0024-4142-18
Bottles of 500 tablets NDC 0024-4142-50
Box of 10 blisters (10 tablets per blister) NDC 0024-4142-10

Store at 25°C (77°F): excursions permitted to 15-30°C (59-86°F), [see USP controlled room temperature].

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

See Medication Guide (17.2)

MULTAQ should be administered with a meal. Warn patients not to take MULTAQ with grapefruit juice.

If a dose is missed, patients should take the next dose at the regularly scheduled time and should not double the dose.

Advise patients to consult a physician if they develop signs or symptoms of worsening heart failure such as acute weight gain, dependent edema, or increasing shortness of breath.

Advise patients to inform their physician of any history of heart failure, rhythm disturbance other than atrial fibrillation or flutter or predisposing conditions such as uncorrected hypokalemia.

MULTAQ may interact with some drugs; therefore, advise patients to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

17.2 Medication Guide

Medication Guide
MULTAQ (MUL-tak)
(dronedarone) Tablets
Rx only

Read this Medication Guide before you start taking MULTAQ and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know before taking MULTAQ?
MULTAQ is not for people with severe heart failure. People with severe heart failure who take MULTAQ have an increased chance of dying. Heart failure means your heart does not pump blood through your body as well as it should.

Do not take MULTAQ if you have severe heart failure:

- **where any physical activity causes shortness of breath or you have shortness of breath while at rest or after a small amount of exercise.**
- **if you were hospitalized for heart failure within the last month even if you are better now.**

Call your doctor right away if you have any signs and symptoms of worsening heart failure:

- shortness of breath or wheezing at rest
- wheezing, chest tightness or coughing up frothy sputum at rest, nighttime or after minor exercise
- trouble sleeping or waking up at night because of breathing problems
- using more pillows to prop yourself up at night so you can breathe more easily
- gaining more than 5 pounds quickly
- increasing swelling of feet or legs

What is MULTAQ?
MULTAQ is a prescription medicine used to lower the chance that you would need to go into the hospital for heart problems. It is meant for people who have had an abnormal heart rhythm called atrial fibrillation or atrial flutter in the last six months but who do not have that abnormal rhythm now or are about to be converted to a normal rhythm. It may be safely used for people who have had atrial fibrillation and atrial flutter who also have medical problems such as high blood pressure, stroke or diabetes.

It is not known if MULTAQ is safe and effective in children younger than age 18 years old.

Who should not take MULTAQ?
See "What is the most important information I should know about taking MULTAQ?"
Do not take MULTAQ if:

- **You have severe heart failure or have recently been in the hospital for heart failure, even if you are better now.**
- **You have severe liver problems.**
- **You take certain medicines that can change the amount of MULTAQ that gets into your body. Do not use these medicines with MULTAQ:**
  - Nefazodone for depression
  - Norvir® (ritonavir) for HIV infection
  - Nizoral® (ketoconazole), and Sporanox® (itraconazole), and Vfend® (voriconazole) for fungal infections
  - Ketek® (telithromycin), Biaxin® (clarithromycin) for bacterial infections
  - Cyclosporine for organ transplant
- **You take certain medicines that can lead to a dangerous abnormal heart rhythm:**
  - Some medicines for mental illness called phenothiazines
  - Some medicines for depression called tricyclic antidepressants
  - Some medicines for abnormal heart rhythm or fast heartbeat
  - Some medicines for bacterial infection

Ask your doctor if you are not sure if your medicine is one that is listed above.

- **You are pregnant or plan to become pregnant.** It is not known if MULTAQ will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- **You are breast-feeding or plan to breastfeed.** It is not known if MULTAQ passes into your breast milk. You and your doctor should decide if you will take MULTAQ or breastfeed. You should not do both.

What should I tell my doctor before starting MULTAQ?

- If you have any other heart problems
- Tell your doctor about all the medicines you take, including any new medicines. Include all prescription and non-prescription medicines, vitamins and herbal remedies. MULTAQ and certain other medicines can react with each other, causing serious side effects.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

Be sure to tell your doctor and pharmacist if you take:

- medicine for high blood pressure, chest pain, or other heart conditions
- statin medicine to lower blood cholesterol
- medicine for TB (tuberculosis)
- medicine for seizures
- medicine for organ transplant
- herbal supplement called St. John's wort

Some of these medicines could keep MULTAQ from working well or make it more likely for you to have side effects.

How should I take MULTAQ?

- Take MULTAQ exactly as your doctor tells you.
- Take MULTAQ two times a day with food, once with your morning meal and once with your evening meal.
- Do not stop taking MULTAQ even if you are feeling well for a long time. The medicine may be working.
- If you miss a dose, wait and take your next dose at your regular time. Do not take 2 doses at the same time. Do not try to make up for a missed dose.

What should I avoid while taking MULTAQ?

Do not drink grapefruit juice while you take MULTAQ. Grapefruit juice can increase the amount of MULTAQ in your blood and increase the likelihood that you will have a side effect of MULTAQ.

What are the possible side effects of MULTAQ?

- slowed heartbeat (bradycardia)
- stomach problems such as
    - diarrhea
    - nausea
    - vomiting
    - stomach area (abdominal) pain
    - indigestion
- feeling tired and weak
- skin problems such as redness, rash, and itching

Tell your doctor about any side effect that bothers you or that does not go away. These are not all the possible side effects of MULTAQ. For more information ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store MULTAQ?

Store MULTAQ at room temperature (59-86°F, or 15-30°C).

Keep MULTAQ and all medicines out of the reach of children.

General information about MULTAQ
Medicines are sometimes used for purposes not mentioned in a Medication Guide. Do not use MULTAQ for a condition for which it was not prescribed. Do not give MULTAQ to other people, even if they have the same symptoms or condition. It may harm them.

This Medication Guide summarizes the most important information about MULTAQ. If you would like more information:

- Talk with your doctor
- Ask your doctor or pharmacist for information about MULTAQ that was written for health-care professionals
- For the latest information and Medication Guide, visit www.sanofi-aventis.us or call sanofi-aventis Medical Information Services at 1-800-633-1610 option 1. The Medication Guide may have changed since this copy was printed.

What are the ingredients in MULTAQ?
Active ingredient: dronedarone
Inactive ingredients: hypromellose, starch, crospovidone, poloxamer 407, lactose monohydrate, colloidal silicon dioxide, magnesium stearate polyethylene glycol 6000, titanium dioxide, carnauba wax

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Rx only
July 2009

Manufactured by Sanofi Winthrop Industrie
1, rue de la Vierge
33440 Ambares, France

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MULTAQ is a trademark of sanofi-aventis.

The brands listed are the registered trademarks of their respective owners and are not trademarks of sanofi-aventis U.S. LLC.

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

sanofi-aventis U.S.
55 Corporate Boulevard
Bridgewater, New Jersey 08807

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

NDA 22-425 Multaq® (dronedarone)

Date of this report:	09-June-2009
Version:	7.0
Status:	Final
Total no. of pages:	18

TABLE OF CONTENTS

NDA 22-425 Multaq® (dronedarone)

sanofi-aventis U.S. 55 Corporate Boulevard
Bridgewater, New Jersey 08807

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

- To prevent Multaq® use in patients with NYHA Class IV heart failure or NYHA Class II-III heart failure with recent decompensation requiring hospitalization or referral to a specialized heart failure clinic by educating prescribers about increased mortality when Multaq® is used in this patient population.
- To inform patients about the serious risks of Multaq®, including increased mortality in patients with severe unstable heart failure.

II. REMS ELEMENTS

A. MEDICATION GUIDE

In accordance with 21 CFR 208.24, sanofi-aventis will ensure that the Medication Guide is available for distribution to patients by providing sufficient numbers to distributors, packers, or authorized dispensers in order to provide a Medication Guide to each patient receiving a sample or a prescription of Multaq®. Sanofi-aventis will institute the following measures:

- The label of each container or package of Multaq® will include a prominent instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed.
- One copy of the Full Prescribing Information that includes a Medication Guide will be provided with each 60-count unit-of-use bottle of Multaq® (a monthly usual supply). Additional Medication Guides will be provided for the 180-count and 500-count bottles as follows:
    - A minimum of 3 Medication Guides will be provided with each 180-count bottle
    - A minimum of 9 Medication Guides will be provided with each 500-count bottle

Medication Guides will be available via sales and/or medical representatives, the product website and through the Sponsor's Medical Information Services Department.

The Medication Guide is appended to this document (see Appendix 1).

B. COMMUNICATION PLAN

In accordance with FDCA 505-1(e) (3), sanofi-aventis will implement a Communication Plan to health care professionals (HCPs) to support implementation of this REMS. The purpose of the Communication Plan is to educate health care professionals on risks associated with the use of Multaq®, the safe and appropriate prescribing information, and the goals of the REMS.

The Elements of the Communication Plan include:

1. *Health Care Professional Information Sheet*

    a. Sanofi-aventis will issue a *Health Care Professional Information Sheet* to targeted health care professionals (key stakeholders and secondary stakeholders as defined below) within 60 days of the REMS approval. This Information Sheet highlights the goals of the Multaq® REMS and actions to ensure appropriate use. Sanofi-aventis will distribute the *Health Care Professional Information Sheet* through hardcopy mailings. In addition, this information will be available through electronic communication (Health Care Notification Network [HCNN]) and made available on the product website.

    b. The *Health Care Professional Information Sheet,* Multaq® Package Insert and Medication Guide will be distributed to HCPs at product launch. These materials will be disseminated every 18 months for at least 3 years. This element of the REMS is not intended to continue over the lifetime of the product; it will function only to inform prescribers of the goals of the Multaq® REMS for a period of 3 years.

The *Health Care Professional Information Sheet* is appended to this document (see Appendix 2).

2. REMS Print Advertising in Professional Society Journals

    a. Sanofi-aventis will issue REMS Print Advertisements in the following professional society journals, monthly for 24 months, following approval of the REMS:

        i. Journal of the American College of Cardiology

        ii. Circulation

        iii. Annals of Internal Medicine

The REMS Print Advertisement is appended to this document (see Appendix 3).

The intended audience for the Communication Plan is:

1. Key stakeholders: Health care professionals, including cardiologists, electrophysiologists, hospitalists, internal medicine and family practice physicians who regularly prescribe antiarrhythmic agents will be targeted. Members of relevant professional societies will also be targeted.

2. Secondary stakeholders: Nurse practitioners and physician assistants who work in offices of the above-mentioned physicians will also be targeted as secondary stakeholders for education.

C. ELEMENTS TO ASSURE SAFE USE

Multaq® can be approved without Elements to Assure Safe Use.

D. IMPLEMENTATION SYSTEM

Multaq® can be used without Elements to Assure Safe Use; therefore, an implementation system is not required.

E. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

Formal assessments of the REMS performance will be provided to the Food and Drug Administration (FDA) annually, years 1-5 and at year 7 post-launch. The first assessment interval will be from August 2009 (product launch) to June 2010. All assessment reports will be submitted to the Agency on the due date as indicated below.

Assessment number	Submission Due Date
1	August 31, 2010
2	August 31, 2011
3	August 31, 2012
4	August 31, 2013
5	August 31, 2014
6	August 31, 2016

APPENDICES OF REMS

1. **Multaq® Medication Guide**
2. **Health Care Professional Information Sheet**
3. **REMS Print Advertisement**

1. MULTAQ® MEDICATION GUIDE

17.2 Medication Guide

Medication Guide

MULTAQ (MUL-tak)

(dronedarone) Tablets

Rx only

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- **where any physical activity causes shortness of breath or you have shortness of breath while at rest or after a small amount of exercise.**
- **if you were hospitalized for heart failure within the last month even if you are better now.**

Call your doctor right away if you have any signs and symptoms of worsening heart failure:

- shortness of breath or wheezing at rest
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What is MULTAQ?

MULTAQ is a prescription medicine used to lower the chance that you would need to go into the hospital for heart problems. It is meant for people who have had an abnormal heart rhythm called atrial fibrillation or atrial flutter in the last six months but who do not have that abnormal rhythm now or are about to be converted to a normal rhythm. It may be safely used for people who have had atrial fibrillation and atrial flutter who also have medical problems such as high blood pressure, stroke or diabetes.

It is not known if MULTAQ is safe and effective in children younger than age 18 years old.

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See "What is the most important information I should know about taking MULTAQ?"

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- **You take certain medicines that can change the amount of MULTAQ that gets into your body. Do not use these medicines with MULTAQ:**
  - Nefazodone for depression
  - Norvir® (ritonavir) for HIV infection
  - Nizoral® (ketoconazole), and Sporanox® (itraconazole), and Vfend® (voriconazole) for fungal infections
  - Ketek® (telithromycin), Biaxin® (clarithromycin) for bacterial infections
  - Cyclosporine for organ transplant
- **You take certain medicines that can lead to a dangerous abnormal heart rhythm:**
  - Some medicines for mental illness called phenothiazines
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  - Some medicines for abnormal heart rhythm or fast heartbeat
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  Ask your doctor if you are not sure if your medicine is one that is listed above.
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What should I tell my doctor before starting MULTAQ?

- If you have any other heart problems
- Tell your doctor about all the medicines you take, including any new medicines. Include all prescription and non-prescription medicines, vitamins and herbal remedies. MULTAQ and certain other medicines can react with each other, causing serious side effects. **Know the medicines you take.** Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

Be sure to tell your doctor and pharmacist if you take:

- medicine for high blood pressure, chest pain, or other heart conditions
- statin medicine to lower blood cholesterol
- medicine for TB (tuberculosis)
- medicine for seizures
- medicine for organ transplant
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Some of these medicines could keep MULTAQ from working well or make it more likely for you to have side effects.

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What should I avoid while taking MULTAQ?

Do not drink grapefruit juice while you take MULTAQ. Grapefruit juice and grapefruit can increase the amount of MULTAQ in your blood and increase the likelihood that you will have a side effect of MULTAQ.

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- Stomach problems such as
    - diarrhea
    - nausea
    - vomiting

  - stomach area (abdominal) pain
  - indigestion
- feeling tired and weak
- skin problems such as redness, rash, and itching

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Keep MULTAQ and all medicines out of the reach of children.

General information about MULTAQ

Medicines are sometimes used for purposes not mentioned in a Medication Guide. Do not use MULTAQ for a condition for which it was not prescribed. Do not give MULTAQ to other people, even if they have the same symptoms or condition. It may harm them.

This Medication Guide summarizes the most important information about MULTAQ. If you would like more information:

- Talk with your doctor
- Ask your doctor or pharmacist for information about MULTAQ that was written for health-care professionals
- For the latest information and Medication Guide, visit www.sanofi-aventis.us or call sanofi-aventis Medical Information Services at 1-800-633-1610 option 1. The Medication Guide may have changed since this copy was printed.

What are the ingredients in MULTAQ?

Active ingredient: dronedarone

Inactive ingredients: hypromellose, starch, crospovidone, poloxamer 407, lactose monohydrate, colloidal silicon dioxide, magnesium stearate polyethylene glycol 6000, titanium dioxide, carnauba wax

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Rx only

Issued month/year

Manufactured by Sanofi Winthrop Industrie

1, rue de la Vierge

33440 Ambares, France

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MULTAQ is a trademark of sanofi-aventis.

The brands listed are the registered trademarks of their respective owners and are not trademarks of sanofi-aventis U.S. LLC.

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

2. MULTAQ® HEALTH CARE PROFESSIONAL INFORMATION SHEET

RISK MITIGATION PROGRAM

MPACT™

MULTAQ® Partnership

for Appropriate Care and Treatment

Health Care Professional Information Sheet for MULTAQ® (dronedarone)

MULTAQ is an antiarrhythmic drug indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AFib) or atrial flutter (AFL), with a recent episode of AFib/AFL and associated cardiovascular risk factors (i.e., age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥50 mm or left ventricular ejection fraction [LVEF] <40%), who are in sinus rhythm or who will be cardioverted.

Do not prescribe MULTAQ for patients with NYHA Class IV heart failure (HF) or NYHA Class II–III HF with recent decompensation requiring hospitalization or referral to a specialized HF clinic

WARNING: HEART FAILURE

MULTAQ is contraindicated in patients with NYHA Class IV heart failure, or NYHA Class II–III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic.

In a placebo-controlled study in patients with severe heart failure requiring recent hospitalization or referral to a specialized heart failure clinic for worsening symptoms (the ANDROMEDA Study), patients given dronedarone had a greater than two-fold increase in mortality. Such patients should not be given dronedarone.

Prescribers should also be aware of other important contraindications, including:

- Coadministration of strong CYP3A4 inhibitors, medicinal products inducing Torsade de Pointes, or Class I or III antiarrhythmic agents
- Second- or third-degree atrioventricular block, sick sinus syndrome (except when used in conjunction with a functioning pacemaker), or bradycardia of <50 bpm
- QTc Bazett ≥500 ms or PR interval >280 ms
- Severe hepatic impairment
- Pregnancy or nursing mothers

RISK MITIGATION PROGRAM

MPACT™

MULTAQ® Partnership
for Appropriate Care and Treatment

Please consider the following *Steps for Ensuring Appropriate Use* when prescribing MULTAQ for your patients:

1. Initiate MULTAQ in appropriate patients

- Screen patients for severity and stability of heart failure; MULTAQ should not be initiated in patients with NYHA Class IV heart failure or NYHA Class II–III heart failure with recent decompensation requiring hospitalization or referral to a specialized heart failure clinic
- Treatment may be initiated in an outpatient or an inpatient setting
- Discontinue use of other Class I or Class III antiarrhythmic therapies
- The dosage of certain cardiovascular medications may need to be adjusted and certain laboratory test changes may occur

2. Counsel patients to report changes in their symptoms and their medications

- Advise patients to consult a physician if they develop signs or symptoms of worsening heart failure such as weight gain, dependent edema, and/or increasing shortness of breath
- Advise patients that MULTAQ should not be taken with certain other medications and to consult with their physicians before starting any new drugs as the dosage of certain cardiovascular medications may need to be adjusted
- Refer patients to the Medication Guide and address any additional questions

3. Check patients for changes in their symptoms or certain lab tests

- Observe patients regularly for signs or symptoms of heart failure that may require additional treatment and/or MULTAQ discontinuation
- Be aware that within a week, MULTAQ causes a small change in serum creatinine that does not reflect a change in underlying renal function

In patients with developing or worsening heart failure during treatment, use clinical judgment to guide the management of each patient based on individual benefit/risk assessment, and consider the suspension or discontinuation of MULTAQ therapy.

Please refer to the enclosed Prescribing Information for complete safety information before prescribing MULTAQ.

Serious Adverse Events:

Health care professionals should report any serious adverse events thought to be associated with MULTAQ use to:

- Sanofi-aventis at 1-800-633-1610 option 2
- FDA's MedWatch reporting system
  - By phone (1-800-FDA-1088)
  - By facsimile (1-800-FDA-0178)
  - Online (https://www.accessdata.fda.gov/scripts/medwatch/)
  - By mail (using the MedWatch Voluntary Reporting form 3500, to the FDA Safety Information and Adverse Event Reporting Program: Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787)

Additional Resources

For additional information:

- Talk to your sanofi-aventis sales representative or call the sanofi-aventis Medical Information Services department at 1-800-633-1610 option 1
- Visit www.MULTAQ.com
- Refer patients to the MULTAQ Medication Guide

sanofi aventis
Because health matters

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3. MULTAQ® REMS PRINT ADVERTISEMENT

sanofi aventis

Because health matters

Important Information on the Use of MULTAQ® (dronedarone)

Do not prescribe MULTAQ for patients with NYHA Class IV heart failure (HF) or NYHA Class II–III HF with recent decompensation requiring hospitalization or referral to a specialized HF clinic

WARNING: HEART FAILURE

MULTAQ is contraindicated in patients with NYHA Class IV heart failure, or NYHA Class II–III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic.

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Sanofi-aventis is committed to appropriate patient care and treatment

The mPACT Program has been developed for health care professionals who will prescribe MULTAQ, in an effort to help ensure appropriate patient selection.

Visit www.MULTAQ.com for more information.

Please see accompanying Brief Summary before prescribing MULTAQ.

RISK MITIGATION PROGRAM

mPACT™

MULTAQ® Partnership for Appropriate Care and Treatment

US.DRO.09.05.016 June 2009
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Temple
7/1/2009 05:17:47 PM

EXHIBIT 6

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,323,493 B1
APPLICATION NO. : 09/446601
DATED : January 29, 2008
INVENTOR(S) : Abramovici et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1, line 1: Insert the following text: -- Cross Reference to Related Applications --.

Column 1, line 2: Insert the following text: -- This application is a 35 U.S.C. § 371 application of PCT International Application No. PCT/FR98/01285 filed June 19, 1998. --.

Column 4, line 37: "$Na_{2\ HPO4}$" should read as -- Na_2HPO_4 --.

Column 4, line 42: Insert the following text: -- The following results were thus obtained: --.

Column 10, Claim 3, line 29: "claim 2" should read as -- claim 1 --.

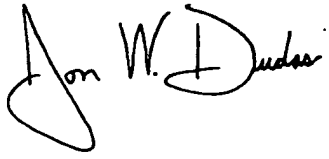
Column 10, Claim 4, line 32: "claim 2" should read as -- claim 1 --.

Column 10, Claim 12, line 59: Cancel the following text: "or a pharmaceutically acceptable salt thereof".

This certificate supersedes the Certificate of Correction issued June 17, 2008.

Signed and Sealed this

Twenty-second Day of July, 2008



JON W. DUDAS
Director of the United States Patent and Trademark Office

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of **Abramovici et al.**

U.S. Patent No.: **7,323,493**

Issued: **January 29, 2008**

Title: **Solid Pharmaceutical Compositions Containing Benzofuran Derivatives**

REQUEST FOR CERTIFICATE OF CORRECTION FOR PTO MISTAKE
UNDER 35 U.S.C. 254 and 37 C.F.R. 1.322

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450
Attn: Certificate of Correction Branch

In the matter of U.S. Patent No. 7,323,493, it is respectfully requested that a Certificate of Correction be issued to cover the following errors which occurred in the printing of the patent:

1. Column 4, line 37 (page 7, line 24 of the Specification): "Na_2 HPO4" should read as --Na_2HPO_4 --.

2. Column 4, line 42 (page 8, line 1 of the Specification): Please insert the following text: --The following results were thus obtained: -- .

Support for the correction of the following errors can be found in the Amendment filed on January 12, 2007, as acknowledged by the Examiner in the Notice of Allowability and Interview Summary (PTOL-413) dated September 19, 2007:

3. Column 1, line 1: Insert the following text: --Cross Reference to Related Applications --.

4. Column 1, line 2: Insert the following text: --This application is a 35 U.S.C. § 371 application of PCT International Application No. PCT/FR98/01285 filed June 19, 1998. --.

5. Claim 3, column 10, line 29 (see claim 2 of Amendment filed January 12, 2007): "claim 2" should read as -- claim 1 --.

6. Claim 4, column 10, line 32 (see claim 3 of Amendment filed January 12, 2007): "claim 2" should read as -- claim 1 --.

7. Claim 12, column 10, line 59 (see claim 20 of Amendment filed January 12, 2007): Cancel the following text: "or a pharmaceutically acceptable salt thereof".

REMARKS

It is respectfully requested that a Certificate of Correction be issued for the above-identified patent. All of the above errors occurred during the printing of the patent and, therefore, no fee is due. However, the Commissioner is hereby authorized to charge any fees that are required by this paper to Deposit Account No. 18-1982.

A copy of the required Certificate of Correction Form PTO-1050 is enclosed.

Respectfully submitted,

March 17, 2008
Date

Kelly L. Bender, Registry No. 52,610
Attorney for Applicant

sanofi-aventis U.S. Inc.
U.S. Patent Operations
Route #202-206 / P.O. Box 6800
Bridgewater, NJ 08807-0800
Telephone (610) 889-8995
Telefax (908) 231-2626

sanofi-aventis Docket No. IVD000994 US PCT

Staple Here Only

Printer's Trim Line

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : **7,323,493**

DATED : **January 29, 2008**

INVENTOR(s) : **Abramovici et al.**

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1, line 1: Insert the following text: --Cross Reference to Related Applications --.

Column 1, line 2: Insert the following text: --This application is a 35 U.S.C. § 371 application of PCT International Application No. PCT/FR98/01285 filed June 19, 1998. --.

Column 4, line 37: "Na_2 HPO4" should read as --Na_2HPO_4 --;

Column 4, line 42: Insert the following text: --The following results were thus obtained: -- .

Claim 3, line 29: "claim 2" should read as -- claim 1 --.

Claim 4, line 32: "claim 2" should read as -- claim 1 --.

Claim 12, line 59: Cancel the following text: "or a pharmaceutically acceptable salt thereof".

Mailing Address of Sender:

Patent No. 7,323,493

Kelly L. Bender, U.S. Patent Operations
sanofi-aventis U.S. Inc.
Route #202-206
P. O. Box 6800
Bridgewater, New Jersey 08807-0800

Certificate of Correction (PTO Form 1050) - Amended

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EXHIBIT 7

Patent Maintenance Fees		07/08/2009 05:47 AM EDT	
Patent Number:	7323493	Application Number:	09446601
Issue Date:	01/29/2008	Filing Date:	04/03/2000
Window Opens:	01/31/2011	Surcharge Date:	08/01/2011
Window Closes:	01/30/2012	Payment Year:	
Entity Status:	LARGE		
Customer Number:	187		
Street Address:	ATTENTION: BREVETS SANOFI-AVENTIS		
City:	ANTONY		
State:			
Zip Code:	92165		
Phone Number:	(+33) 557-6530		
Currently there are no fees due.			

Return To:

USPTO Home Page

Finance Online Shopping Page

United States Patent and Trademark Office

Patent Bibliographic Data				07/08/2009 05:48 AM	
Patent Number:	7323493			**Application Number:**	09446601
Issue Date:	01/29/2008			**Filing Date:**	04/03/2000
Title:	SOLID PHARMACEUTICAL COMPOSITIONS CONTAINING BENZOFURANE DERIVATIVES				
Status:	4th year fee window opens: 01/31/2011			**Entity:**	Large
Window Opens:	01/31/2011	**Surcharge Date:**	08/01/2011	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:	1551	MAINTENANCE FEE DUE AT 3.5 YEARS			
Surcharge Fee Code:					
Most recent events (up to 7):	09/24/2008	Payor Number Assigned. --- End of Maintenance History ---			
Address for fee purposes:	ATTENTION: BREVETS SANOFI-AVENTIS 20 AVENUE RAYMOND ANTONY, 92165				

Run Another Query

United States Patent and Trademark Office

Maintenance Fees Window Dates

07/08/2009 05:48 AM EDT

Patent Number: 7323493

Application Number: 09446601

	4th Year	8th Year	12th Year
Open Date	01/31/2011	01/29/2015	01/29/2019
Surcharge Date	08/01/2011	07/30/2015	07/30/2019
Close Date	01/30/2012	01/29/2016	01/29/2020

EXHIBIT 8

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 48,344

JUL 20 1995

Sanofi Recherche
Attention: G.C.J. Martin, Ph.D.
Centre de Montpellier
371, Rue du Professeur Blayac
34184 Montpellier Cedex 04
France

Dear Dr. Martin:

We acknowledge receipt of your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 48,344

Sponsor: Sanofi Recherche

Name of Drug: SR33589B

Date of Submission: July 7, 1995

Date of Receipt: July 11, 1995

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in your IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations). These responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon as possible and in no event later than 10 working days after initial receipt of the information and reporting any unexpected fatal or

life-threatening experience to the FDA by telephone no later than three working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified with IND number 48,344, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this IND, please call me at (301) 594-5300

Sincerely yours,

Diana Willard

Diana Willard
Consumer Safety Officer
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Clementi & Associates
Attention: W.A. Clementi, Pharm.D., F.C.P.
290 King of Prussia Road
Radnor, PA 19087

EXHIBIT 9

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 49,484

JAN - 3 1996

Sanofi Winthrop, Inc.
Attn: George A. Clay, Ph.D.
9 Great Valley Parkway
P. O. Box 3026
Malvern, VA 19355

Dear Sir/Madam:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying information:

IND Number Assigned: 49,484

Sponsor: Sanofi Winthrop, Inc.

Name of Drug: SR 33589B Oral

Date of Submission: Dec. 26, 1995

Date of Receipt: Dec. 26, 1995

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30-day period, we determine that serious deficiencies in your IND require correction before human studies can begin or that would require restriction of human studies until correction, we will notify you immediately by telephone. In that event, we expect that you will withhold or restrict such studies until we notify you that the material you have submitted to correct the deficiencies is satisfactory.

A sponsor of an IND may obtain supplies of the investigational drug upon notification of our receipt of the application. Sponsors, however, may not ship the investigational drug to investigators named in the IND until 30 days after the receipt date.

The 30-day restriction does not apply if the IND number was assigned for emergency use of the drug.

RECEIVED

JAN 10 1996

GEORGE A. CLAY

FORM FDA 3228a (5/89)

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act. These responsibilities include reporting any unexpected fatal or life-threatening experience to us by telephone no later than three working days after receipt of the information, reporting adverse reactions that are both serious and unexpected in writing within ten days and submitting progress reports at least annually.

Please forward all future communications concerning this IND in TRIPLICATE, IDENTIFIED WITH THE IND NUMBER and addressed as follows:

Please see enclosure for addresses.

Should you have any questions concerning this IND, please call:

Diana Willard

Consumer Safety Officer
(301) 443-4730

Sincerely Yours,

Diana M. Willard
for

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I

cc: Original File - pink
Division File - yellow
Division CSO - blue

ACKNOWLEDGEMENT

ADDRESS FOR ORIGINAL SUBMISSIONS (INDs AND NDAs):

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CENTRAL DOCUMENT ROOM
PARK BLDG., ROOM 214
12420 PARKLAWN DRIVE
ROCKVILLE, MD 20852

ADDRESS FOR AMENDMENTS (INDs AND NDAs) VIA U.S. POSTAL SERVICE:

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
ATTENTION: DOCUMENT CONTROL ROOM, HFD-110
5600 FISHERS LANE
ROCKVILLE, MD 20857

ADDRESS FOR AMENDMENTS (INDs AND NDAs) VIA OVERNIGHT MAIL AND UPS DELIVERIES:

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
ATTENTION: DOCUMENT CONTROL ROOM, HFD-110
1451 ROCKVILLE PIKE
ROCKVILLE, MD 20852

EXHIBIT 10

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-913

Sanofi-Synthelabo Inc.
Attention: Douglas A. Greene, M.D.
11 Great Valley Parkway
P.O. Box 3026
Malverna, PA 19355

Dear Dr. Greene:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Dronedarone hydrochloride 400 mg Tablets
Review Priority Classification:	Standard (S)
Date of Application:	June 10, 2005
Date of Receipt:	June 10, 2005
Our Reference Number:	NDA 21-913

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 9, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 10, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the deferral granted on April 1, 2005, for the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to one of the following address:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

Mr. Russell Fortney
Regulatory Health Project Manager
(301) 594-5311

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Edward Fromm
7/19/05 01:28:34 PM

EXHIBIT 11

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-425

sanofi-aventis U.S., LLC
Attention: Jon Villaume, Ph.D.
Vice President, Regulatory Affairs
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Villaume:

We have received your new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Multaq (dronedarone hydrochloride) Tablets 400 mg
Review Priority Classification:	Priority (P)
Date of Application:	June 27, 2008
Receipt Date of User Fees:	July 31, 2008
Our Reference Number:	NDA 22-425

This application was considered incomplete and was not accepted for filing because all fees owed for this application were not paid. Subsequently, we received on July 31, 2008 all fees due. The receipt date for fees due is considered the new receipt date for this application.

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 29, 2008, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 31, 2009.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products

5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Russell Fortney, Regulatory Health Project Manager, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Edward Fromm
8/6/2008 12:09:28 PM

EXHIBIT 12

IND 48,344 History Log

Date Sent	Serial Number	Component Category
13-Feb-1994		OTH OTHER/MISC./UNKNOWN
17-Jun-1994		OTH OTHER/MISC./UNKNOWN
09-Jan-1995		OTH OTHER/MISC./UNKNOWN
13-Jan-1995		OTH OTHER/MISC./UNKNOWN
23-Mar-1995		OTH OTHER/MISC./UNKNOWN
04-Apr-1995		OTH OTHER/MISC./UNKNOWN
24-May-1995		MOM MINUTES OF MEETING
24-May-1995		OTH OTHER/MISC./UNKNOWN
09-Jun-1995		OTH OTHER/MISC./UNKNOWN
30-Jun-1995		OTH OTHER/MISC./UNKNOWN
07-Jul-1995	000	INITIAL IND
17-Jul-1995		OTH OTHER/MISC./UNKNOWN
20-Jul-1995		OTH OTHER/MISC./UNKNOWN
24-Jul-1995	001	OTH OTHER/MISC./UNKNOWN
25-Jul-1995		MOM MINUTES OF MEETING
26-Jul-1995		OTH OTHER/MISC./UNKNOWN
31-Jul-1995		OTH OTHER/MISC./UNKNOWN
02-Aug-1995		OTH OTHER/MISC./UNKNOWN
03-Aug-1995		OTH OTHER/MISC./UNKNOWN
08-Aug-1995		OTH OTHER/MISC./UNKNOWN
10-Aug-1995		OTH OTHER/MISC./UNKNOWN
22-Aug-1995	002	OTH OTHER/MISC./UNKNOWN
30-Aug-1995	003	OTH OTHER/MISC./UNKNOWN
20-Sep-1995	004	OTH OTHER/MISC./UNKNOWN
29-Sep-1995		OTH OTHER/MISC./UNKNOWN
25-Oct-1995		OTH OTHER/MISC./UNKNOWN
26-Oct-1995	005	RCR RESPONSE TO COMMENT REQUEST
01-Nov-1995		OTH OTHER/MISC./UNKNOWN
27-Dec-1995	006	PC PROTOCOL CHANGE
11-Jan-1996	007	ADR ADVERSE DRUG REACTION
17-Jan-1996	008	PC PROTOCOL CHANGE
15-May-1996		OTH OTHER/MISC./UNKNOWN
04-Jun-1996	009	ADR ADVERSE DRUG REACTION
11-Jun-1996	010	ADR ADVERSE DRUG REACTION
10-Jul-1996	011	PC PROTOCOL CHANGE
06-Aug-1996	012	PRE PRE CLINICAL INFORMATION
19-Aug-1996	013	ADR ADVERSE DRUG REACTION
06-Sep-1996		OTH OTHER/MISC./UNKNOWN
10-Sep-1996		OTH OTHER/MISC./UNKNOWN

30-Sep-1996	014	RCR RESPONSE TO COMMENT REQUEST
11-Oct-1996	015	AR ANNUAL REPORT
04-Nov-1996		OTH OTHER/MISC./UNKNOWN
06-Nov-1996		OTH OTHER/MISC./UNKNOWN
14-Nov-1996		OTH OTHER/MISC./UNKNOWN
18-Nov-1996	016	RCR RESPONSE TO COMMENT REQUEST
27-Jan-1997		REA REQUEST EXPORT AUTHORIZ.
30-Jan-1997	017	PC PROTOCOL CHANGE
07-Feb-1997	018	GC GENERAL CORRESPONDENCE
14-Feb-1997		OTH OTHER/MISC./UNKNOWN
12-Aug-1997	019	CMC CMC INFORMATION
07-Oct-1997	020	AR ANNUAL REPORT
24-Nov-1997		OTH OTHER/MISC./UNKNOWN
11-Feb-1998		ADR ADVERSE DRUG REACTION
25-Feb-1998	021	ADR ADVERSE DRUG REACTION
03-Apr-1998		ADR ADVERSE DRUG REACTION
09-Apr-1998	022	GC GENERAL CORRESPONDENCE
13-Apr-1998	023	ADR ADVERSE DRUG REACTION
17-Apr-1998	024	GC GENERAL CORRESPONDENCE
05-May-1998		OTH OTHER/MISC./UNKNOWN
06-May-1998	025	GC GENERAL CORRESPONDENCE
27-May-1998		OTH OTHER/MISC./UNKNOWN
10-Jul-1998	026	GC GENERAL CORRESPONDENCE
21-Jul-1998		OTH OTHER/MISC./UNKNOWN
29-Jul-1998	027	GC GENERAL CORRESPONDENCE
30-Sep-1998		OTH OTHER/MISC./UNKNOWN
18-Feb-1999		OTH OTHER/MISC./UNKNOWN
26-Feb-1999	028	GC GENERAL CORRESPONDENCE
01-Mar-1999	029	AR ANNUAL REPORT
11-Mar-1999	030	FSR FINAL STUDY REPORT
11-Mar-1999		OTH OTHER/MISC./UNKNOWN
18-Mar-1999	031	PRE PRE CLINICAL INFORMATION
14-Apr-1999	032	FSR FINAL STUDY REPORT
19-Apr-1999		OTH OTHER/MISC./UNKNOWN
22-Apr-1999		OTH OTHER/MISC./UNKNOWN
10-May-1999		OTH OTHER/MISC./UNKNOWN
12-May-1999	033	GC GENERAL CORRESPONDENCE

19-May-1999		OTH OTHER/MISC./UNKNOWN
02-Jun-1999		OTH OTHER/MISC./UNKNOWN
09-Jul-1999	034	FSR FINAL STUDY REPORT
29-Jul-1999	035	GC GENERAL CORRESPONDENCE
12-Aug-1999	036	GC GENERAL CORRESPONDENCE
20-Aug-1999	037	ADR ADVERSE DRUG REACTION
01-Sep-1999	038	GC GENERAL CORRESPONDENCE
15-Sep-1999		OTH OTHER/MISC./UNKNOWN
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01-Oct-1999	040	FSR FINAL STUDY REPORT
29-Dec-1999	041	ADR ADVERSE DRUG REACTION
21-Jan-2000	042	PRE PRE CLINICAL INFORMATION
09-Feb-2000	043	FSR FINAL STUDY REPORT
29-Feb-2000	044	AR ANNUAL REPORT
06-Oct-2000	045	ADR ADVERSE DRUG REACTION
10-Oct-2000	046	ADR ADVERSE DRUG REACTION
19-Oct-2000		ADR ADVERSE DRUG REACTION
24-Oct-2000	047	ADR ADVERSE DRUG REACTION
01-Nov-2000	048	OTH OTHER/MISC./UNKNOWN
22-Nov-2000	049	FSR FINAL STUDY REPORT
29-Dec-2000	050	ADR ADVERSE DRUG REACTION
28-Feb-2001	051	AR ANNUAL REPORT
31-Aug-2001	052	ADR ADVERSE DRUG REACTION
07-Sep-2001	053	PRE PRE CLINICAL INFORMATION
09-Jan-2002	054	GC GENERAL CORRESPONDENCE
22-Feb-2002		ADR ADVERSE DRUG REACTION
28-Feb-2002	055	AR ANNUAL REPORT
01-Mar-2002	056	ADR ADVERSE DRUG REACTION
08-Apr-2002		OTH OTHER/MISC./UNKNOWN
10-Apr-2002	057	FSR FINAL STUDY REPORT
25-Apr-2002	058	ADR ADVERSE DRUG REACTION
01-May-2002	059	ADR ADVERSE DRUG REACTION
01-May-2002	060	ADR ADVERSE DRUG REACTION
16-May-2002	061	ADR ADVERSE DRUG REACTION
21-May-2002	062	ADR ADVERSE DRUG REACTION
10-Jun-2002	063	ADR ADVERSE DRUG REACTION
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27-Aug-2002	066	ADR ADVERSE DRUG REACTION
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17-Sep-2002	069	ADR ADVERSE DRUG REACTION
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03-Oct-2002	071	ADR ADVERSE DRUG REACTION
09-Oct-2002	072	ADR ADVERSE DRUG REACTION
21-Oct-2002	073	ADR ADVERSE DRUG REACTION
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19-Nov-2002	079	ADR ADVERSE DRUG REACTION
21-Nov-2002		ADR ADVERSE DRUG REACTION
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26-Nov-2002	080	ADR ADVERSE DRUG REACTION
13-Dec-2002	081	ADR ADVERSE DRUG REACTION
17-Dec-2002	082	ADR ADVERSE DRUG REACTION
20-Dec-2002	083	ADR ADVERSE DRUG REACTION
24-Dec-2002	084	ADR ADVERSE DRUG REACTION
24-Dec-2002	085	ADR ADVERSE DRUG REACTION
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02-Jan-2003	086	ADR ADVERSE DRUG REACTION
02-Jan-2003	087	ADR ADVERSE DRUG REACTION
03-Jan-2003	088	ADR ADVERSE DRUG REACTION
09-Jan-2003	089	IB INVESTIGATOR'S BROCHURE
05-Feb-2003	090	ADR ADVERSE DRUG REACTION
10-Feb-2003	091	ADR ADVERSE DRUG REACTION
11-Feb-2003	092	ADR ADVERSE DRUG REACTION
12-Feb-2003		ADR ADVERSE DRUG REACTION
13-Feb-2003	093	ADR ADVERSE DRUG REACTION
28-Feb-2003	094	AR ANNUAL REPORT
18-Mar-2003	095	ADR ADVERSE DRUG REACTION
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31-Mar-2003	098	ADR ADVERSE DRUG REACTION
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21-May-2003	100	ADR ADVERSE DRUG REACTION

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02-Jun-2003	104	ADR ADVERSE DRUG REACTION
06-Jun-2003	102	ADR ADVERSE DRUG REACTION
26-Jun-2003	103	ADR ADVERSE DRUG REACTION
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25-Nov-2003	106	ADR ADVERSE DRUG REACTION
23-Jan-2004	107	ADR ADVERSE DRUG REACTION
27-Feb-2004	108	AR ANNUAL REPORT
26-Mar-2004	109	ADR ADVERSE DRUG REACTION
12-Oct-2004	110	ADR ADVERSE DRUG REACTION
05-Jan-2005	111	ADR ADVERSE DRUG REACTION
28-Feb-2005	112	AR ANNUAL REPORT
09-May-2005	113	IA INFORMATION AMENDMENT
23-Jun-2005		ADR ADVERSE DRUG REACTION
06-Oct-2005	114	ADR ADVERSE DRUG REACTION
07-Nov-2005	115	ADR ADVERSE DRUG REACTION
16-Nov-2005	116	ADR ADVERSE DRUG REACTION
30-Nov-2005	117	ADR ADVERSE DRUG REACTION
01-Dec-2005	118	ADR ADVERSE DRUG REACTION
08-Dec-2005	119	ADR ADVERSE DRUG REACTION
15-Dec-2005	120	ADR ADVERSE DRUG REACTION
05-Jan-2006	121	ADR ADVERSE DRUG REACTION
13-Jan-2006	122	ADR ADVERSE DRUG REACTION
19-Jan-2006	123	ADR ADVERSE DRUG REACTION
23-Jan-2006	124	OTH OTHER/MISC./UNKNOWN
23-Jan-2006	125	OTH OTHER/MISC./UNKNOWN
08-Feb-2006		OTH OTHER/MISC./UNKNOWN
28-Feb-2006	126	AR ANNUAL REPORT
29-Mar-2006	127	ADR ADVERSE DRUG REACTION
12-Apr-2006	128	ADR ADVERSE DRUG REACTION
26-May-2006	129	ADR ADVERSE DRUG REACTION
05-Jun-2006	130	ADR ADVERSE DRUG REACTION
13-Jul-2006	131	ADR ADVERSE DRUG REACTION
25-Jul-2006	132	ADR ADVERSE DRUG REACTION
07-Aug-2006	133	ADR ADVERSE DRUG REACTION
27-Sep-2006	134	ADR ADVERSE DRUG REACTION
05-Oct-2006	135	ADR ADVERSE DRUG REACTION
01-Nov-2006	136	ADR ADVERSE DRUG REACTION
13-Nov-2006	137	ADR ADVERSE DRUG REACTION
28-Nov-2006	138	ADR ADVERSE DRUG REACTION
30-Nov-2006	139	ADR ADVERSE DRUG REACTION
04-Dec-2006	140	ADR ADVERSE DRUG REACTION
08-Dec-2006	141	ADR ADVERSE DRUG REACTION

18-Dec-2006	142	ADR ADVERSE DRUG REACTION
21-Dec-2006	143	ADR ADVERSE DRUG REACTION
21-Dec-2006	144	ADR ADVERSE DRUG REACTION
28-Dec-2006	145	ADR ADVERSE DRUG REACTION
02-Jan-2007	146	ADR ADVERSE DRUG REACTION
22-Jan-2007	147	ADR ADVERSE DRUG REACTION
22-Jan-2007	148	ADR ADVERSE DRUG REACTION
06-Feb-2007	149	ADR ADVERSE DRUG REACTION
08-Feb-2007	150	ADR ADVERSE DRUG REACTION
01-Mar-2007	151	AR ANNUAL REPORT
01-Mar-2007	152	ADR ADVERSE DRUG REACTION
29-Mar-2007	153	ADR ADVERSE DRUG REACTION
29-Mar-2007	154	ADR ADVERSE DRUG REACTION
09-Apr-2007	155	ADR ADVERSE DRUG REACTION
10-Apr-2007	156	ADR ADVERSE DRUG REACTION
13-Apr-2007	157	ADR ADVERSE DRUG REACTION
11-May-2007	158	ADR ADVERSE DRUG REACTION
11-May-2007	159	ADR ADVERSE DRUG REACTION
17-May-2007	160	ADR ADVERSE DRUG REACTION
18-May-2007	161	ADR ADVERSE DRUG REACTION
22-May-2007	162	ADR ADVERSE DRUG REACTION
25-May-2007	163	ADR ADVERSE DRUG REACTION
05-Jun-2007	164	ADR ADVERSE DRUG REACTION
25-Jun-2007	165	ADR ADVERSE DRUG REACTION
27-Jul-2007	166	ADR ADVERSE DRUG REACTION
04-Sep-2007	167	ADR ADVERSE DRUG REACTION
04-Sep-2007		ADR ADVERSE DRUG REACTION
06-Sep-2007	168	ADR ADVERSE DRUG REACTION
18-Sep-2007	169	ADR ADVERSE DRUG REACTION
18-Sep-2007		ADR ADVERSE DRUG REACTION
26-Sep-2007	170	ADR ADVERSE DRUG REACTION
27-Sep-2007	171	ADR ADVERSE DRUG REACTION
17-Oct-2007	172	ADR ADVERSE DRUG REACTION
20-Nov-2007	173	ADR ADVERSE DRUG REACTION
12-Dec-2007	174	ADR ADVERSE DRUG REACTION
25-Jan-2008	175	ADR ADVERSE DRUG REACTION
15-Feb-2008	176	ADR ADVERSE DRUG REACTION
19-Feb-2008	177	ADR ADVERSE DRUG REACTION
27-Feb-2008	178	AR ANNUAL REPORT
04-Mar-2008	179	ADR ADVERSE DRUG REACTION
06-Mar-2008	180	ADR ADVERSE DRUG REACTION
12-Mar-2008	181	ADR ADVERSE DRUG REACTION
07-Apr-2008	182	ADR ADVERSE DRUG REACTION

18-Apr-2008	183	ADR ADVERSE DRUG REACTION
22-Apr-2008	184	ADR ADVERSE DRUG REACTION
12-May-2008	185	ADR ADVERSE DRUG REACTION
16-May-2008	186	ADR ADVERSE DRUG REACTION
21-May-2008	187	ADR ADVERSE DRUG REACTION
27-Jun-2008	188	ADR ADVERSE DRUG REACTION
15-Sep-2008	189	ADR ADVERSE DRUG REACTION
24-Oct-2008	190	ADR ADVERSE DRUG REACTION
24-Oct-2008		ADR ADVERSE DRUG REACTION
12-Nov-2008	191	ADR ADVERSE DRUG REACTION
18-Nov-2008	192	ADR ADVERSE DRUG REACTION
18-Nov-2008		ADR ADVERSE DRUG REACTION
25-Nov-2008	193	ADR ADVERSE DRUG REACTION
27-Feb-2009	194	AR ANNUAL REPORT

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Date Sent	Serial Number	Component Category
26-Dec-1995	000	INITIAL IND
03-Jan-1996		ROS RECEIPT OF SUBMISSION
26-Jan-1996		OTH OTHER/MISC./UNKNOWN
02-May-1996		OTH OTHER/MISC./UNKNOWN
03-May-1996	001	NI NEW INVESTIGATOR
15-May-1996		OTH OTHER/MISC./UNKNOWN
04-Jun-1996	002	ADR ADVERSE DRUG REACTION
11-Jun-1996	003	ADR ADVERSE DRUG REACTION
08-Jul-1996	004	PC PROTOCOL CHANGE
08-Aug-1996	005	FSR FINAL STUDY REPORT
16-Aug-1996	006	NP NEW PROTOCOL
19-Aug-1996	007	ADR ADVERSE DRUG REACTION
06-Sep-1996		OTH OTHER/MISC./UNKNOWN
10-Sep-1996		OTH OTHER/MISC./UNKNOWN
11-Sep-1996	008	ADR ADVERSE DRUG REACTION
11-Sep-1996	009	NI NEW INVESTIGATOR
13-Sep-1996	010	CMC CMC INFORMATION
25-Sep-1996	011	RCR RESPONSE TO COMMENT REQUEST
07-Oct-1996	012	CMC CMC INFORMATION
27-Jan-1997		REA REQUEST EXPORT AUTHORIZ.
30-Jan-1997	013	PC PROTOCOL CHANGE
07-Feb-1997	014	GC GENERAL CORRESPONDENCE
14-Feb-1997		OTH OTHER/MISC./UNKNOWN
11-Mar-1997		OTH OTHER/MISC./UNKNOWN
13-Mar-1997	015	NI NEW INVESTIGATOR
26-Mar-1997	016	AR ANNUAL REPORT
16-Apr-1997	017	NI NEW INVESTIGATOR
22-May-1997		GC GENERAL CORRESPONDENCE
22-May-1997		REA REQUEST EXPORT AUTHORIZ.
27-May-1997		AEA APPROVED EXPORT AUTHORIZ.
27-May-1997		GC GENERAL CORRESPONDENCE
27-May-1997		OTH OTHER/MISC./UNKNOWN
25-Jun-1997	018	FSR FINAL STUDY REPORT
25-Jun-1997	019	PRE PRE CLINICAL INFORMATION
18-Jul-1997	020	PRE PRE CLINICAL INFORMATION
18-Jul-1997	021	FSR FINAL STUDY REPORT

21-Aug-1997	022	PRE PRE CLINICAL INFORMATION
23-Sep-1997	023	PRE PRE CLINICAL INFORMATION
31-Oct-1997	024	ADR ADVERSE DRUG REACTION
06-Nov-1997		ADR ADVERSE DRUG REACTION
06-Nov-1997		OTH OTHER/MISC./UNKNOWN
12-Nov-1997	025	ADR ADVERSE DRUG REACTION
17-Nov-1997	026	PC PROTOCOL CHANGE
24-Nov-1997		OTH OTHER/MISC./UNKNOWN
25-Feb-1998	027	GC GENERAL CORRESPONDENCE
31-Mar-1998	028	PRE PRE CLINICAL INFORMATION
31-Mar-1998	029	FSR FINAL STUDY REPORT
01-Apr-1998	030	GC GENERAL CORRESPONDENCE
13-Apr-1998	031	GC GENERAL CORRESPONDENCE
17-Apr-1998	032	AR ANNUAL REPORT
05-May-1998	033	PRE PRE CLINICAL INFORMATION
05-May-1998		OTH OTHER/MISC./UNKNOWN
27-May-1998		OTH OTHER/MISC./UNKNOWN
12-Jun-1998	034	NI NEW INVESTIGATOR
01-Jul-1998		GC GENERAL CORRESPONDENCE
03-Jul-1998		ADR ADVERSE DRUG REACTION
10-Jul-1998	035	ADR ADVERSE DRUG REACTION
21-Jul-1998		ADR ADVERSE DRUG REACTION
21-Jul-1998		OTH OTHER/MISC./UNKNOWN
29-Jul-1998	036	ADR ADVERSE DRUG REACTION
12-Aug-1998		REA REQUEST EXPORT AUTHORIZ.
18-Aug-1998	037	NI NEW INVESTIGATOR
25-Aug-1998		AEA APPROVED EXPORT AUTHORIZ.
27-Aug-1998	038	GC GENERAL CORRESPONDENCE
30-Sep-1998		OTH OTHER/MISC./UNKNOWN
18-Feb-1999		ADR ADVERSE DRUG REACTION
18-Feb-1999		OTH OTHER/MISC./UNKNOWN
26-Feb-1999	039	ADR ADVERSE DRUG REACTION
01-Mar-1999	040	AR ANNUAL REPORT
03-Mar-1999	041	RFM REQUEST FOR MTG
11-Mar-1999	042	FSR FINAL STUDY REPORT
11-Mar-1999		OTH OTHER/MISC./UNKNOWN
15-Mar-1999		OTH OTHER/MISC./UNKNOWN
15-Mar-1999		OTH OTHER/MISC./UNKNOWN
18-Mar-1999	043	PRE PRE CLINICAL INFORMATION

18-Mar-1999		OTH OTHER/MISC./UNKNOWN
23-Mar-1999	044	GC GENERAL CORRESPONDENCE
23-Mar-1999	045	RCR RESPONSE TO COMMENT REQUEST
01-Apr-1999		OTH OTHER/MISC./UNKNOWN
14-Apr-1999	046	FSR FINAL STUDY REPORT
19-Apr-1999		OTH OTHER/MISC./UNKNOWN
22-Apr-1999		OTH OTHER/MISC./UNKNOWN
06-May-1999		OTH OTHER/MISC./UNKNOWN
07-May-1999		OTH OTHER/MISC./UNKNOWN
07-May-1999		OTH OTHER/MISC./UNKNOWN
10-May-1999		OTH OTHER/MISC./UNKNOWN
12-May-1999	047	PMP PRE-MEETING PACKAGE
12-May-1999	048	ADR ADVERSE DRUG REACTION
19-May-1999		OTH OTHER/MISC./UNKNOWN
02-Jun-1999		OTH OTHER/MISC./UNKNOWN
04-Jun-1999	049	MOM MINUTES OF MEETING
11-Jun-1999		MOM MINUTES OF MEETING
16-Jun-1999	050	RCR RESPONSE TO COMMENT REQUEST
09-Jul-1999	051	FSR FINAL STUDY REPORT
29-Jul-1999	052	ADR ADVERSE DRUG REACTION
12-Aug-1999	053	NP NEW PROTOCOL
12-Aug-1999	054	CMC CMC INFORMATION
12-Aug-1999	055	GC GENERAL CORRESPONDENCE
20-Aug-1999	056	ADR ADVERSE DRUG REACTION
01-Sep-1999	057	GC GENERAL CORRESPONDENCE
15-Sep-1999		GC GENERAL CORRESPONDENCE
01-Oct-1999	058	FSR FINAL STUDY REPORT
01-Oct-1999	059	FSR FINAL STUDY REPORT
13-Oct-1999	060	OTH OTHER/MISC./UNKNOWN
04-Nov-1999		OTH OTHER/MISC./UNKNOWN
29-Dec-1999	061	ADR ADVERSE DRUG REACTION
21-Jan-2000	062	PRE PRE CLINICAL INFORMATION
09-Feb-2000	063	FSR FINAL STUDY REPORT
29-Feb-2000	064	AR ANNUAL REPORT
04-May-2000	065	PRE PRE CLINICAL INFORMATION
18-May-2000		OTH OTHER/MISC./UNKNOWN
23-May-2000		OTH OTHER/MISC./UNKNOWN
23-May-2000		OTH OTHER/MISC./UNKNOWN
28-Jun-2000	066	PC PROTOCOL CHANGE

31-Aug-2000	067	NI NEW INVESTIGATOR
06-Oct-2000	068	ADR ADVERSE DRUG REACTION
09-Oct-2000	069	NI NEW INVESTIGATOR
10-Oct-2000	070	ADR ADVERSE DRUG REACTION
19-Oct-2000		ADR ADVERSE DRUG REACTION
24-Oct-2000	071	ADR ADVERSE DRUG REACTION
01-Nov-2000	072	OTH OTHER/MISC./UNKNOWN
22-Nov-2000	073	FSR FINAL STUDY REPORT
22-Nov-2000	074	NI NEW INVESTIGATOR
29-Dec-2000	075	ADR ADVERSE DRUG REACTION
28-Feb-2001	076	AR ANNUAL REPORT
19-Mar-2001		GC GENERAL CORRESPONDENCE
20-Mar-2001	077	RFM REQUEST FOR MTG
21-Mar-2001		OTH OTHER/MISC./UNKNOWN
26-Mar-2001	078	PMP PRE-MEETING PACKAGE
30-Mar-2001	079	NI NEW INVESTIGATOR
27-Apr-2001	080	MOM MINUTES OF MEETING
29-May-2001		MOM MINUTES OF MEETING
29-May-2001		OTH OTHER/MISC./UNKNOWN
12-Jun-2001	081	GC GENERAL CORRESPONDENCE
12-Jul-2001	082	NI NEW INVESTIGATOR
24-Jul-2001		OTH OTHER/MISC./UNKNOWN
31-Aug-2001	083	ADR ADVERSE DRUG REACTION
05-Sep-2001		MOM MINUTES OF MEETING
07-Sep-2001	084	PRE PRE CLINICAL INFORMATION
12-Sep-2001	085	NP NEW PROTOCOL
14-Sep-2001	086	CMC CMC INFORMATION
12-Oct-2001		OTH OTHER/MISC./UNKNOWN
16-Oct-2001	087	RCR RESPONSE TO COMMENT REQUEST
15-Nov-2001	088	PC PROTOCOL CHANGE
16-Nov-2001	089	RCR RESPONSE TO COMMENT REQUEST
21-Nov-2001	090	PC PROTOCOL CHANGE
23-Nov-2001		MOM MINUTES OF MEETING
23-Nov-2001		OTH OTHER/MISC./UNKNOWN
23-Nov-2001		OTH OTHER/MISC./UNKNOWN
28-Nov-2001		RCR RESPONSE TO COMMENT REQUEST
28-Nov-2001		OTH OTHER/MISC./UNKNOWN
28-Nov-2001		OTH OTHER/MISC./UNKNOWN
20-Dec-2001	091	NI NEW INVESTIGATOR
26-Dec-2001		OTH OTHER/MISC./UNKNOWN

26-Dec-2001		OTH OTHER/MISC./UNKNOWN
09-Jan-2002	092	OTH OTHER/MISC./UNKNOWN
10-Jan-2002	093	NP NEW PROTOCOL
21-Jan-2002	094	NI NEW INVESTIGATOR
25-Feb-2002	095	NI NEW INVESTIGATOR
28-Feb-2002	096	AR ANNUAL REPORT
28-Feb-2002	096	IB INVESTIGATOR'S BROCHURE
01-Mar-2002	097	ADR ADVERSE DRUG REACTION
19-Mar-2002	098	NP NEW PROTOCOL
26-Mar-2002	099	NI NEW INVESTIGATOR
02-Apr-2002	100	OTH OTHER/MISC./UNKNOWN
03-Apr-2002	101	FSR FINAL STUDY REPORT
04-Apr-2002		RCR RESPONSE TO COMMENT REQUEST
09-Apr-2002	102	GC GENERAL CORRESPONDENCE
11-Apr-2002	103	NP NEW PROTOCOL
23-Apr-2002		ADR ADVERSE DRUG REACTION
25-Apr-2002	104	ADR ADVERSE DRUG REACTION
25-Apr-2002	105	NI NEW INVESTIGATOR
01-May-2002	106	ADR ADVERSE DRUG REACTION
01-May-2002	107	ADR ADVERSE DRUG REACTION
03-May-2002		OTH OTHER/MISC./UNKNOWN
10-May-2002		OTH OTHER/MISC./UNKNOWN
16-May-2002	108	ADR ADVERSE DRUG REACTION
20-May-2002		MOM MINUTES OF MEETING
20-May-2002		MOM MINUTES OF MEETING
21-May-2002	109	ADR ADVERSE DRUG REACTION
30-May-2002		ADR ADVERSE DRUG REACTION
31-May-2002	110	NI NEW INVESTIGATOR
03-Jun-2002	111	RCR RESPONSE TO COMMENT REQUEST
03-Jun-2002	112	RCR RESPONSE TO COMMENT REQUEST
07-Jun-2002		MOM MINUTES OF MEETING
10-Jun-2002	113	ADR ADVERSE DRUG REACTION
11-Jun-2002		OTH OTHER/MISC./UNKNOWN
26-Jun-2002	114	NI NEW INVESTIGATOR
10-Jul-2002	115	PC PROTOCOL CHANGE
11-Jul-2002	116	RCR RESPONSE TO COMMENT REQUEST
17-Jul-2002	117	RCR RESPONSE TO COMMENT REQUEST
22-Jul-2002		ADR ADVERSE DRUG REACTION
23-Jul-2002	118	NI NEW INVESTIGATOR

30-Jul-2002	119	ADR ADVERSE DRUG REACTION
02-Aug-2002	120	ADR ADVERSE DRUG REACTION
19-Aug-2002		ADR ADVERSE DRUG REACTION
27-Aug-2002	121	ADR ADVERSE DRUG REACTION
30-Aug-2002	122	CMC CMC INFORMATION
06-Sep-2002	123	ADR ADVERSE DRUG REACTION
11-Sep-2002	124	ADR ADVERSE DRUG REACTION
17-Sep-2002	125	ADR ADVERSE DRUG REACTION
18-Sep-2002	126	NI NEW INVESTIGATOR
18-Sep-2002		ADR ADVERSE DRUG REACTION
27-Sep-2002	127	ADR ADVERSE DRUG REACTION
03-Oct-2002	128	ADR ADVERSE DRUG REACTION
09-Oct-2002	129	ADR ADVERSE DRUG REACTION
21-Oct-2002	130	ADR ADVERSE DRUG REACTION
22-Oct-2002	131	FSR FINAL STUDY REPORT
30-Oct-2002	132	ADR ADVERSE DRUG REACTION
30-Oct-2002	133	NI NEW INVESTIGATOR
01-Nov-2002		ADR ADVERSE DRUG REACTION
06-Nov-2002	134	ADR ADVERSE DRUG REACTION
06-Nov-2002		OTH OTHER/MISC./UNKNOWN
07-Nov-2002		ADR ADVERSE DRUG REACTION
12-Nov-2002	135	ADR ADVERSE DRUG REACTION
15-Nov-2002	136	ADR ADVERSE DRUG REACTION
19-Nov-2002	137	ADR ADVERSE DRUG REACTION
21-Nov-2002		ADR ADVERSE DRUG REACTION
21-Nov-2002		ADR ADVERSE DRUG REACTION
22-Nov-2002		OTH OTHER/MISC./UNKNOWN
26-Nov-2002	138	ADR ADVERSE DRUG REACTION
10-Dec-2002	139	PC PROTOCOL CHANGE
13-Dec-2002	140	ADR ADVERSE DRUG REACTION
17-Dec-2002	141	ADR ADVERSE DRUG REACTION
20-Dec-2002	142	ADR ADVERSE DRUG REACTION
20-Dec-2002		OTH OTHER/MISC./UNKNOWN
24-Dec-2002	143	ADR ADVERSE DRUG REACTION
24-Dec-2002	144	ADR ADVERSE DRUG REACTION
24-Dec-2002		ADR ADVERSE DRUG REACTION
02-Jan-2003	145	ADR ADVERSE DRUG REACTION
02-Jan-2003	146	ADR ADVERSE DRUG REACTION
03-Jan-2003	147	ADR ADVERSE DRUG REACTION
07-Jan-2003	148	IB INVESTIGATOR'S BROCHURE
13-Jan-2003	149	OTH OTHER/MISC./UNKNOWN
27-Jan-2003	150	ADR ADVERSE DRUG REACTION
27-Jan-2003	151	OTH OTHER/MISC./UNKNOWN

30-Jan-2003	152	NSI NEW SUB-INVESTIGATOR
05-Feb-2003	153	ADR ADVERSE DRUG REACTION
05-Feb-2003	154	RFM REQUEST FOR MTG
07-Feb-2003		OTH OTHER/MISC./UNKNOWN
10-Feb-2003	155	ADR ADVERSE DRUG REACTION
12-Feb-2003		ADR ADVERSE DRUG REACTION
13-Feb-2003	156	ADR ADVERSE DRUG REACTION
13-Feb-2003		RFM REQUEST FOR MTG
28-Feb-2003	157	AR ANNUAL REPORT
06-Mar-2003	158	PC PROTOCOL CHANGE
11-Mar-2003	159	NI NEW INVESTIGATOR
12-Mar-2003	160	RFM REQUEST FOR MTG
12-Mar-2003		RFM REQUEST FOR MTG
18-Mar-2003	161	FSR FINAL STUDY REPORT
18-Mar-2003	162	ADR ADVERSE DRUG REACTION
19-Mar-2003		OTH OTHER/MISC./UNKNOWN
24-Mar-2003	163	ADR ADVERSE DRUG REACTION
24-Mar-2003		ADR ADVERSE DRUG REACTION
28-Mar-2003		ADR ADVERSE DRUG REACTION
31-Mar-2003	164	ADR ADVERSE DRUG REACTION
31-Mar-2003	165	ADR ADVERSE DRUG REACTION
04-Apr-2003	166	ADR ADVERSE DRUG REACTION
04-Apr-2003		ADR ADVERSE DRUG REACTION
16-Apr-2003		RFM REQUEST FOR MTG
17-Apr-2003	167	OTH OTHER/MISC./UNKNOWN
29-Apr-2003	168	FSR FINAL STUDY REPORT
02-May-2003		OTH OTHER/MISC./UNKNOWN
07-May-2003	169	NI NEW INVESTIGATOR
21-May-2003	170	ADR ADVERSE DRUG REACTION
22-May-2003		MOM MINUTES OF MEETING
27-May-2003	171	ADR ADVERSE DRUG REACTION
28-May-2003	172	GC GENERAL CORRESPONDENCE
06-Jun-2003	173	ADR ADVERSE DRUG REACTION
11-Jun-2003	174	FSR FINAL STUDY REPORT
25-Jun-2003	175	NI NEW INVESTIGATOR
26-Jun-2003	176	ADR ADVERSE DRUG REACTION
02-Jul-2003	177	ADR ADVERSE DRUG REACTION
15-Aug-2003	178	ADR ADVERSE DRUG REACTION
12-Sep-2003	179	NSI NEW SUB-INVESTIGATOR
23-Sep-2003	180	FSR FINAL STUDY REPORT
29-Sep-2003	181	OTH OTHER/MISC./UNKNOWN
16-Oct-2003	182	PRE PRE CLINICAL INFORMATION

21-Nov-2003	183	PRE PRE CLINICAL INFORMATION
25-Nov-2003	184	ADR ADVERSE DRUG REACTION
23-Dec-2003	185	FSR FINAL STUDY REPORT
23-Jan-2004	186	ADR ADVERSE DRUG REACTION
10-Feb-2004	187	NSI NEW SUB-INVESTIGATOR
27-Feb-2004	188	AR ANNUAL REPORT
04-Mar-2004	189	PRE PRE CLINICAL INFORMATION
25-Mar-2004	190	CMC CMC INFORMATION
26-Mar-2004	191	ADR ADVERSE DRUG REACTION
14-May-2004	192	RFM REQUEST FOR MTG
17-May-2004	193	NSI NEW SUB-INVESTIGATOR
17-May-2004		CMC CMC INFORMATION
17-May-2004		OTH OTHER/MISC./UNKNOWN
18-May-2004		OTH OTHER/MISC./UNKNOWN
19-May-2004		OTH OTHER/MISC./UNKNOWN
20-May-2004	194	RCR RESPONSE TO COMMENT REQUEST
20-May-2004		OTH OTHER/MISC./UNKNOWN
15-Jun-2004	195	PMP PRE-MEETING PACKAGE
23-Jun-2004	196	FSR FINAL STUDY REPORT
01-Jul-2004	197	NP NEW PROTOCOL
29-Jul-2004		OTH OTHER/MISC./UNKNOWN
12-Aug-2004		MOM MINUTES OF MEETING
12-Oct-2004	198	ADR ADVERSE DRUG REACTION
14-Oct-2004	199	RFM REQUEST FOR MTG
25-Oct-2004		RFM REQUEST FOR MTG
26-Oct-2004		OTH OTHER/MISC./UNKNOWN
26-Oct-2004		RFM REQUEST FOR MTG
28-Oct-2004	200	NP NEW PROTOCOL
09-Nov-2004	201	GC GENERAL CORRESPONDENCE
19-Nov-2004		OTH OTHER/MISC./UNKNOWN
30-Nov-2004		OTH OTHER/MISC./UNKNOWN
08-Dec-2004	202	PMP PRE-MEETING PACKAGE
13-Dec-2004	203	NI NEW INVESTIGATOR
13-Dec-2004		OTH OTHER/MISC./UNKNOWN
13-Dec-2004		OTH OTHER/MISC./UNKNOWN
16-Dec-2004		APL APPROVAL LETTER
16-Dec-2004		OTH OTHER/MISC./UNKNOWN
16-Dec-2004		OTH OTHER/MISC./UNKNOWN
20-Dec-2004		OTH OTHER/MISC./UNKNOWN
20-Dec-2004		OTH OTHER/MISC./UNKNOWN
05-Jan-2005	204	ADR ADVERSE DRUG REACTION
05-Jan-2005	205	MOM MINUTES OF MEETING

24-Jan-2005		OTH OTHER/MISC./UNKNOWN
04-Feb-2005		OTH OTHER/MISC./UNKNOWN
07-Feb-2005		OTH OTHER/MISC./UNKNOWN
24-Feb-2005	206	CMC CMC INFORMATION
28-Feb-2005	207	AR ANNUAL REPORT
09-Mar-2005	208	PED PEDIATRIC INFORMATION
09-Mar-2005	209	OTH OTHER/MISC./UNKNOWN
09-Mar-2005	210	RFM REQUEST FOR MTG
10-Mar-2005		OTH OTHER/MISC./UNKNOWN
11-Mar-2005	211	OTH OTHER/MISC./UNKNOWN
21-Mar-2005		OTH OTHER/MISC./UNKNOWN
21-Mar-2005		OTH OTHER/MISC./UNKNOWN
21-Mar-2005		PED PEDIATRIC INFORMATION
29-Mar-2005		OTH OTHER/MISC./UNKNOWN
01-Apr-2005		OTH OTHER/MISC./UNKNOWN
01-Apr-2005		PED PEDIATRIC INFORMATION
05-Apr-2005		OTH OTHER/MISC./UNKNOWN
25-Apr-2005	212	NP NEW PROTOCOL
09-May-2005	213	IB INVESTIGATOR'S BROCHURE
23-May-2005		GC GENERAL CORRESPONDENCE
23-May-2005		RFC REQUEST FOR COMMENTS
23-Jun-2005	214	CMC CMC INFORMATION
06-Jul-2005		ROS RECEIPT OF SUBMISSION
14-Jul-2005		IB INVESTIGATOR'S BROCHURE
14-Jul-2005		OTH OTHER/MISC./UNKNOWN
27-Jul-2005		OTH OTHER/MISC./UNKNOWN
29-Jul-2005		OTH OTHER/MISC./UNKNOWN
01-Aug-2005	215	NI NEW INVESTIGATOR
01-Aug-2005		OTH OTHER/MISC./UNKNOWN
10-Aug-2005	216	PC PROTOCOL CHANGE
06-Sep-2005	217	FSR FINAL STUDY REPORT
07-Sep-2005	218	NI NEW INVESTIGATOR
06-Oct-2005	219	ADR ADVERSE DRUG REACTION
11-Oct-2005		IAP INITIAL APPLICATION
12-Oct-2005		IB INVESTIGATOR'S BROCHURE
07-Nov-2005	220	ADR ADVERSE DRUG REACTION
16-Nov-2005	221	NI NEW INVESTIGATOR
16-Nov-2005	222	ADR ADVERSE DRUG REACTION
18-Nov-2005	223	PC PROTOCOL CHANGE
30-Nov-2005	224	ADR ADVERSE DRUG REACTION
01-Dec-2005	225	ADR ADVERSE DRUG REACTION
06-Dec-2005	226	CMC CMC INFORMATION

08-Dec-2005	227	ADR ADVERSE DRUG REACTION
08-Dec-2005		ADR ADVERSE DRUG REACTION
13-Dec-2005		OTH OTHER/MISC./UNKNOWN
15-Dec-2005	228	ADR ADVERSE DRUG REACTION
16-Dec-2005	229	CMC CMC INFORMATION
19-Dec-2005	230	NI NEW INVESTIGATOR
05-Jan-2006	231	ADR ADVERSE DRUG REACTION
13-Jan-2006	232	ADR ADVERSE DRUG REACTION
19-Jan-2006	233	ADR ADVERSE DRUG REACTION
23-Jan-2006	234	OTH OTHER/MISC./UNKNOWN
23-Jan-2006	235	OTH OTHER/MISC./UNKNOWN
07-Feb-2006	236	NI NEW INVESTIGATOR
08-Feb-2006		OTH OTHER/MISC./UNKNOWN
28-Feb-2006	237	AR ANNUAL REPORT
15-Mar-2006	238	PC PROTOCOL CHANGE
28-Mar-2006	239	ADR ADVERSE DRUG REACTION
28-Mar-2006	239	NI NEW INVESTIGATOR
29-Mar-2006	240	ADR ADVERSE DRUG REACTION
12-Apr-2006	241	ADR ADVERSE DRUG REACTION
09-May-2006	242	NI NEW INVESTIGATOR
26-May-2006	243	ADR ADVERSE DRUG REACTION
05-Jun-2006	244	ADR ADVERSE DRUG REACTION
12-Jun-2006	245	NI NEW INVESTIGATOR
13-Jul-2006	246	NI NEW INVESTIGATOR
13-Jul-2006	247	ADR ADVERSE DRUG REACTION
25-Jul-2006	248	ADR ADVERSE DRUG REACTION
07-Aug-2006	249	ADR ADVERSE DRUG REACTION
07-Aug-2006	250	NI NEW INVESTIGATOR
23-Aug-2006	251	NI NEW INVESTIGATOR
29-Aug-2006	252	PC PROTOCOL CHANGE
21-Sep-2006	253	RCR RESPONSE TO COMMENT REQUEST
25-Sep-2006	254	NI NEW INVESTIGATOR
27-Sep-2006	255	ADR ADVERSE DRUG REACTION
05-Oct-2006	256	ADR ADVERSE DRUG REACTION
24-Oct-2006	257	OTH OTHER/MISC./UNKNOWN
25-Oct-2006	258	NI NEW INVESTIGATOR
01-Nov-2006	259	ADR ADVERSE DRUG REACTION
13-Nov-2006	260	ADR ADVERSE DRUG REACTION
15-Nov-2006	261	FSR FINAL STUDY REPORT
28-Nov-2006	262	ADR ADVERSE DRUG REACTION
30-Nov-2006	263	ADR ADVERSE DRUG REACTION
04-Dec-2006	264	ADR ADVERSE DRUG REACTION

08-Dec-2006	265	ADR ADVERSE DRUG REACTION
13-Dec-2006	266	NI NEW INVESTIGATOR
18-Dec-2006	267	ADR ADVERSE DRUG REACTION
19-Dec-2006		OTH OTHER/MISC./UNKNOWN
21-Dec-2006	268	ADR ADVERSE DRUG REACTION
21-Dec-2006	269	ADR ADVERSE DRUG REACTION
28-Dec-2006	270	ADR ADVERSE DRUG REACTION
02-Jan-2007	271	ADR ADVERSE DRUG REACTION
22-Jan-2007	272	ADR ADVERSE DRUG REACTION
22-Jan-2007	273	ADR ADVERSE DRUG REACTION
23-Jan-2007	274	PC PROTOCOL CHANGE
23-Jan-2007		OTH OTHER/MISC./UNKNOWN
06-Feb-2007	275	ADR ADVERSE DRUG REACTION
08-Feb-2007	276	ADR ADVERSE DRUG REACTION
09-Feb-2007	277	OTH OTHER/MISC./UNKNOWN
09-Feb-2007	278	NP NEW PROTOCOL
09-Feb-2007	279	IB INVESTIGATOR'S BROCHURE
20-Feb-2007		ADR ADVERSE DRUG REACTION
23-Feb-2007	280	PC PROTOCOL CHANGE
27-Feb-2007		OTH OTHER/MISC./UNKNOWN
01-Mar-2007	281	AR ANNUAL REPORT
01-Mar-2007	282	ADR ADVERSE DRUG REACTION
01-Mar-2007		OTH OTHER/MISC./UNKNOWN
02-Mar-2007		OTH OTHER/MISC./UNKNOWN
26-Mar-2007	283	RCR RESPONSE TO COMMENT REQUEST
28-Mar-2007		ADR ADVERSE DRUG REACTION
28-Mar-2007		OTH OTHER/MISC./UNKNOWN
29-Mar-2007	284	ADR ADVERSE DRUG REACTION
29-Mar-2007	285	ADR ADVERSE DRUG REACTION
09-Apr-2007	286	ADR ADVERSE DRUG REACTION
10-Apr-2007	287	ADR ADVERSE DRUG REACTION
13-Apr-2007	288	ADR ADVERSE DRUG REACTION
13-Apr-2007		OTH OTHER/MISC./UNKNOWN
01-May-2007	289	CMC CMC INFORMATION
11-May-2007	290	ADR ADVERSE DRUG REACTION
11-May-2007	291	ADR ADVERSE DRUG REACTION
14-May-2007		ADR ADVERSE DRUG REACTION
17-May-2007	292	ADR ADVERSE DRUG REACTION
18-May-2007	293	ADR ADVERSE DRUG REACTION
22-May-2007	294	ADR ADVERSE DRUG REACTION
25-May-2007	295	ADR ADVERSE DRUG REACTION
05-Jun-2007	296	ADR ADVERSE DRUG REACTION

20-Jun-2007	297	NI NEW INVESTIGATOR
25-Jun-2007	298	ADR ADVERSE DRUG REACTION
27-Jul-2007	299	ADR ADVERSE DRUG REACTION
07-Aug-2007	300	NI NEW INVESTIGATOR
21-Aug-2007	301	NI NEW INVESTIGATOR
04-Sep-2007	302	ADR ADVERSE DRUG REACTION
04-Sep-2007		ADR ADVERSE DRUG REACTION
06-Sep-2007	303	ADR ADVERSE DRUG REACTION
18-Sep-2007	304	NI NEW INVESTIGATOR
18-Sep-2007	305	ADR ADVERSE DRUG REACTION
18-Sep-2007		ADR ADVERSE DRUG REACTION
26-Sep-2007	306	ADR ADVERSE DRUG REACTION
27-Sep-2007	307	ADR ADVERSE DRUG REACTION
04-Oct-2007	308	NI NEW INVESTIGATOR
17-Oct-2007	309	NI NEW INVESTIGATOR
17-Oct-2007	310	ADR ADVERSE DRUG REACTION
14-Nov-2007	311	NI NEW INVESTIGATOR
20-Nov-2007	312	ADR ADVERSE DRUG REACTION
12-Dec-2007	313	ADR ADVERSE DRUG REACTION
19-Dec-2007	314	NI NEW INVESTIGATOR
02-Jan-2008	315	OTH OTHER/MISC./UNKNOWN
18-Jan-2008	316	NI NEW INVESTIGATOR
25-Jan-2008	317	ADR ADVERSE DRUG REACTION
15-Feb-2008	318	ADR ADVERSE DRUG REACTION
19-Feb-2008	319	ADR ADVERSE DRUG REACTION
20-Feb-2008	320	NI NEW INVESTIGATOR
27-Feb-2008	321	AR ANNUAL REPORT
04-Mar-2008	322	ADR ADVERSE DRUG REACTION
06-Mar-2008	323	ADR ADVERSE DRUG REACTION
11-Mar-2008	324	RFM REQUEST FOR MTG
12-Mar-2008	325	ADR ADVERSE DRUG REACTION
03-Apr-2008	326	NI NEW INVESTIGATOR
07-Apr-2008	327	ADR ADVERSE DRUG REACTION
18-Apr-2008	328	ADR ADVERSE DRUG REACTION
22-Apr-2008	329	ADR ADVERSE DRUG REACTION
07-May-2008	330	NSI NEW SUB-INVESTIGATOR
12-May-2008	331	GC GENERAL CORRESPONDENCE
12-May-2008	332	ADR ADVERSE DRUG REACTION
16-May-2008	333	ADR ADVERSE DRUG REACTION
21-May-2008	334	ADR ADVERSE DRUG REACTION
06-Jun-2008	335	GC GENERAL CORRESPONDENCE
17-Jun-2008	336	NI NEW INVESTIGATOR

27-Jun-2008	337	ADR ADVERSE DRUG REACTION
16-Jul-2008	338	NI NEW INVESTIGATOR
13-Aug-2008	339	NI NEW INVESTIGATOR
03-Sep-2008	340	OTH OTHER/MISC./UNKNOWN
15-Sep-2008	341	ADR ADVERSE DRUG REACTION
17-Sep-2008	342	NI NEW INVESTIGATOR
24-Oct-2008	343	ADR ADVERSE DRUG REACTION
24-Oct-2008		ADR ADVERSE DRUG REACTION
03-Nov-2008	344	NI NEW INVESTIGATOR
12-Nov-2008	345	ADR ADVERSE DRUG REACTION
18-Nov-2008	346	ADR ADVERSE DRUG REACTION
20-Nov-2008	347	IB INVESTIGATOR'S BROCHURE
25-Nov-2008	348	ADR ADVERSE DRUG REACTION
05-Jan-2009	349	OTH OTHER/MISC./UNKNOWN
27-Jan-2009	350	NI NEW INVESTIGATOR
06-Feb-2009	351	NP NEW PROTOCOL
17-Feb-2009	352	OTH OTHER/MISC./UNKNOWN
20-Feb-2009	353	CMC CMC INFORMATION
27-Feb-2009	354	AR ANNUAL REPORT
19-May-2009	355	NSI NEW SUB-INVESTIGATOR
25-Jun-2009	356	OTH OTHER/MISC./UNKNOWN

EXHIBIT 13

NDA 21-913 History Log

Date Sent	Component Category	Amend/Supplement
29-Mar-2005	PED PEDIATRIC INFORMATION	
10-Jun-2005	OAP ORIG. APPLICAT. NDA/AND	000
10-Jun-2005	CMC CMC INFORMATION	
06-Jul-2005	ROS RECEIPT OF SUBMISSION	
13-Jul-2005	OTH OTHER/MISC./UNKNOWN	
13-Jul-2005	OTH OTHER/MISC./UNKNOWN	
14-Jul-2005	OTH OTHER/MISC./UNKNOWN	
19-Jul-2005	ROS RECEIPT OF SUBMISSION	
19-Jul-2005	GC GENERAL CORRESPONDENCE	
22-Jul-2005	RCR RESPONSE TO COMMENT REQUEST	001
27-Jul-2005	OTH OTHER/MISC./UNKNOWN	
29-Jul-2005	OTH OTHER/MISC./UNKNOWN	
01-Aug-2005	OTH OTHER/MISC./UNKNOWN	
05-Aug-2005	RCR RESPONSE TO COMMENT REQUEST	002
09-Aug-2005	RFC REQUEST FOR COMMENTS	
09-Aug-2005	CMC CMC INFORMATION	003
10-Aug-2005	OTH OTHER/MISC./UNKNOWN	
10-Aug-2005	OTH OTHER/MISC./UNKNOWN	
17-Aug-2005	RCR RESPONSE TO COMMENT REQUEST	004
22-Aug-2005	OTH OTHER/MISC./UNKNOWN	

23-Aug-2005	GC GENERAL CORRESPONDENCE	
23-Aug-2005	GC GENERAL CORRESPONDENCE	
31-Aug-2005	DMF DRUG MASTER FILE	
04-Oct-2005	LB LABELING	005
11-Oct-2005	SU SAFETY UPDATE	
11-Oct-2005	SU SAFETY UPDATE	006
14-Oct-2005	OTH OTHER/MISC./UNKNOWN	
18-Oct-2005	OTH OTHER/MISC./UNKNOWN	
21-Oct-2005	OTH OTHER/MISC./UNKNOWN	
21-Oct-2005	OTH OTHER/MISC./UNKNOWN	
18-Nov-2005	PMP PRE-MEETING PACKAGE	
05-Dec-2005	OTH OTHER/MISC./UNKNOWN	
05-Dec-2005	RCR RESPONSE TO COMMENT REQUEST	007
06-Dec-2005	CMC CMC INFORMATION	008
08-Dec-2005	OTH OTHER/MISC./UNKNOWN	
15-Dec-2005	OTH OTHER/MISC./UNKNOWN	
15-Dec-2005	OTH OTHER/MISC./UNKNOWN	
15-Dec-2005	OTH OTHER/MISC./UNKNOWN	
22-Dec-2005	RCR RESPONSE TO COMMENT REQUEST	009
03-Jan-2006	OTH OTHER/MISC./UNKNOWN	010
26-Jan-2006	OTH OTHER/MISC./UNKNOWN	011
26-Jan-2006	OTH OTHER/MISC./UNKNOWN	012

15-Feb-2006	OTH OTHER/MISC./UNKNOWN	
16-Feb-2006	RCR RESPONSE TO COMMENT REQUEST	013
27-Feb-2006	RCR RESPONSE TO COMMENT REQUEST	014
06-Mar-2006	RCR RESPONSE TO COMMENT REQUEST	015
08-Mar-2006	RCR RESPONSE TO COMMENT REQUEST	016
20-Mar-2006	OTH OTHER/MISC./UNKNOWN	
21-Mar-2006	OTH OTHER/MISC./UNKNOWN	
03-May-2006	OTH OTHER/MISC./UNKNOWN	
22-May-2006	OTH OTHER/MISC./UNKNOWN	
01-Jun-2006	OTH OTHER/MISC./UNKNOWN	
19-Jun-2006	OTH OTHER/MISC./UNKNOWN	
29-Jun-2006	OTH OTHER/MISC./UNKNOWN	
19-Jul-2006	OTH OTHER/MISC./UNKNOWN	
29-Aug-2006	OTH OTHER/MISC./UNKNOWN	
05-Sep-2006	GC GENERAL CORRESPONDENCE	017
13-Apr-2007	OTH OTHER/MISC./UNKNOWN	
18-May-2007	OTH OTHER/MISC./UNKNOWN	
23-Jan-2008	LB LABELING	
31-Jan-2008	OTH OTHER/MISC./UNKNOWN	
06-Feb-2008	RFM REQUEST FOR MTG	
12-Feb-2008	OTH OTHER/MISC./UNKNOWN	
15-Feb-2008	OTH OTHER/MISC./UNKNOWN	

26-Feb-2008	PMP PRE-MEETING PACKAGE	
31-Mar-2008	OTH OTHER/MISC./UNKNOWN	
07-Apr-2008	OTH OTHER/MISC./UNKNOWN	
08-Apr-2008	OTH OTHER/MISC./UNKNOWN	
10-Apr-2008	OTH OTHER/MISC./UNKNOWN	
12-May-2008	OTH OTHER/MISC./UNKNOWN	
27-Jun-2008	RCR RESPONSE TO COMMENT REQUEST	
27-Jun-2008	OTH OTHER/MISC./UNKNOWN	
27-Jun-2008	OTH OTHER/MISC./UNKNOWN	
14-Jul-2008	RCR RESPONSE TO COMMENT REQUEST	
21-Jul-2008	RCR RESPONSE TO COMMENT REQUEST	
23-Jul-2008	RFC REQUEST FOR COMMENTS	
25-Jul-2008	OTH OTHER/MISC./UNKNOWN	
28-Jul-2008	OTH OTHER/MISC./UNKNOWN	
29-Jul-2008	OTH OTHER/MISC./UNKNOWN	
30-Jul-2008	MOM MINUTES OF MEETING	
30-Jul-2008	OTH OTHER/MISC./UNKNOWN	
31-Jul-2008	OTH OTHER/MISC./UNKNOWN	
06-Aug-2008	ROS RECEIPT OF SUBMISSION	

NDA 22-425 History Log

Date Sent	Component Category	Amend/Supplement
31-Jul-2008	OAP ORIG. APPLICAT. NDA/AND	000
06-Aug-2008	ROS RECEIPT OF SUBMISSION	
06-Aug-2008	OTH OTHER/MISC./UNKNOWN	
06-Aug-2008	UF USER FEE	
12-Aug-2008	PRE PRE CLINICAL INFORMATION	
13-Aug-2008	RCR RESPONSE TO COMMENT REQUEST	001
13-Aug-2008	RCR RESPONSE TO COMMENT REQUEST	
14-Aug-2008	PRE PRE CLINICAL INFORMATION	
15-Aug-2008	RCR RESPONSE TO COMMENT REQUEST	
15-Aug-2008	RFC REQUEST FOR COMMENTS	
19-Aug-2008	PED PEDIATRIC INFORMATION	
20-Aug-2008	OTH OTHER/MISC./UNKNOWN	
25-Aug-2008	GCL GENERAL CLINICAL	
28-Aug-2008	OTH OTHER/MISC./UNKNOWN	
29-Aug-2008	OTH OTHER/MISC./UNKNOWN	
11-Sep-2008	RCR RESPONSE TO COMMENT REQUEST	
11-Sep-2008	OTH OTHER/MISC./UNKNOWN	
24-Sep-2008	OTH OTHER/MISC./UNKNOWN	
29-Sep-2008	OTH OTHER/MISC./UNKNOWN	

29-Sep-2008	OTH OTHER/MISC./UNKNOWN	
02-Oct-2008	RFM REQUEST FOR MTG	
03-Oct-2008	OTH OTHER/MISC./UNKNOWN	
03-Oct-2008	OTH OTHER/MISC./UNKNOWN	
03-Oct-2008	RFM REQUEST FOR MTG	
06-Oct-2008	OTH OTHER/MISC./UNKNOWN	
06-Oct-2008	RFM REQUEST FOR MTG	
08-Oct-2008	OTH OTHER/MISC./UNKNOWN	
08-Oct-2008	OTH OTHER/MISC./UNKNOWN	
09-Oct-2008	OTH OTHER/MISC./UNKNOWN	
09-Oct-2008	RFC REQUEST FOR COMMENTS	
09-Oct-2008	RFC REQUEST FOR COMMENTS	
14-Oct-2008	OTH OTHER/MISC./UNKNOWN	
14-Oct-2008	OTH OTHER/MISC./UNKNOWN	
15-Oct-2008	OTH OTHER/MISC./UNKNOWN	
16-Oct-2008	OTH OTHER/MISC./UNKNOWN	
17-Oct-2008	RCR RESPONSE TO COMMENT REQUEST	
21-Oct-2008	RFC REQUEST FOR COMMENTS	
27-Oct-2008	RFM REQUEST FOR MTG	
27-Oct-2008	GC GENERAL CORRESPONDENCE	
27-Oct-2008	OTH OTHER/MISC./UNKNOWN	
27-Oct-2008	OTH OTHER/MISC./UNKNOWN	

31-Oct-2008	RCR RESPONSE TO COMMENT REQUEST	
03-Nov-2008	PED PEDIATRIC INFORMATION	
04-Nov-2008	RFC REQUEST FOR COMMENTS	
05-Nov-2008	OTH OTHER/MISC./UNKNOWN	
07-Nov-2008	RFC REQUEST FOR COMMENTS	
10-Nov-2008	RCR RESPONSE TO COMMENT REQUEST	
11-Nov-2008	RCR RESPONSE TO COMMENT REQUEST	
14-Nov-2008	RCR RESPONSE TO COMMENT REQUEST	
17-Nov-2008	OTH OTHER/MISC./UNKNOWN	
19-Nov-2008	RFC REQUEST FOR COMMENTS	
19-Nov-2008	RFM REQUEST FOR MTG	
20-Nov-2008	SU SAFETY UPDATE	
24-Nov-2008	OTH OTHER/MISC./UNKNOWN	
02-Dec-2008	RCR RESPONSE TO COMMENT REQUEST	
03-Dec-2008	RCR RESPONSE TO COMMENT REQUEST	
08-Dec-2008	RFC REQUEST FOR COMMENTS	
10-Dec-2008	RFM REQUEST FOR MTG	
17-Dec-2008	RCR RESPONSE TO COMMENT REQUEST	
18-Dec-2008	UF USER FEE	
19-Dec-2008	RCR RESPONSE TO COMMENT REQUEST	
24-Dec-2008	RCR RESPONSE TO COMMENT REQUEST	
29-Dec-2008	OTH OTHER/MISC./UNKNOWN	

02-Jan-2009	OTH OTHER/MISC./UNKNOWN	
08-Jan-2009	RFC REQUEST FOR COMMENTS	
13-Jan-2009	RFC REQUEST FOR COMMENTS	
14-Jan-2009	OTH OTHER/MISC./UNKNOWN	
16-Jan-2009	OTH OTHER/MISC./UNKNOWN	
21-Jan-2009	RFC REQUEST FOR COMMENTS	
22-Jan-2009	OTH OTHER/MISC./UNKNOWN	
22-Jan-2009	LB LABELING	
22-Jan-2009	OTH OTHER/MISC./UNKNOWN	
27-Jan-2009	OTH OTHER/MISC./UNKNOWN	
27-Jan-2009	RCR RESPONSE TO COMMENT REQUEST	
28-Jan-2009	MOM MINUTES OF MEETING	
28-Jan-2009	OTH OTHER/MISC./UNKNOWN	
28-Jan-2009	RCR RESPONSE TO COMMENT REQUEST	
29-Jan-2009	RCR RESPONSE TO COMMENT REQUEST	
30-Jan-2009	MOM MINUTES OF MEETING	
30-Jan-2009	OTH OTHER/MISC./UNKNOWN	
30-Jan-2009	OTH OTHER/MISC./UNKNOWN	
05-Feb-2009	RCR RESPONSE TO COMMENT REQUEST	
06-Feb-2009	OTH OTHER/MISC./UNKNOWN	
07-Feb-2009	OTH OTHER/MISC./UNKNOWN	
09-Feb-2009	RCR RESPONSE TO COMMENT REQUEST	

09-Feb-2009	OTH OTHER/MISC./UNKNOWN	
10-Feb-2009	OTH OTHER/MISC./UNKNOWN	
10-Feb-2009	OTH OTHER/MISC./UNKNOWN	
10-Feb-2009	OTH OTHER/MISC./UNKNOWN	
11-Feb-2009	OTH OTHER/MISC./UNKNOWN	
11-Feb-2009	OTH OTHER/MISC./UNKNOWN	
12-Feb-2009	OTH OTHER/MISC./UNKNOWN	
12-Feb-2009	OTH OTHER/MISC./UNKNOWN	
13-Feb-2009	OTH OTHER/MISC./UNKNOWN	
13-Feb-2009	OTH OTHER/MISC./UNKNOWN	
13-Feb-2009	LB LABELING	
13-Feb-2009	PMP PRE-MEETING PACKAGE	
19-Feb-2009	OTH OTHER/MISC./UNKNOWN	
19-Feb-2009	RCR RESPONSE TO COMMENT REQUEST	
20-Feb-2009	OTH OTHER/MISC./UNKNOWN	
23-Feb-2009	OTH OTHER/MISC./UNKNOWN	
23-Feb-2009	OTH OTHER/MISC./UNKNOWN	
23-Feb-2009	OTH OTHER/MISC./UNKNOWN	
23-Feb-2009	RCR RESPONSE TO COMMENT REQUEST	
23-Feb-2009	LB LABELING	
26-Feb-2009	RCR RESPONSE TO COMMENT REQUEST	
27-Feb-2009	RCR RESPONSE TO COMMENT REQUEST	

27-Feb-2009	OTH OTHER/MISC./UNKNOWN	
10-Mar-2009	RCR RESPONSE TO COMMENT REQUEST	
16-Mar-2009	PMP PRE-MEETING PACKAGE	
16-Mar-2009	RCR RESPONSE TO COMMENT REQUEST	
17-Mar-2009	OTH OTHER/MISC./UNKNOWN	
20-Mar-2009	LB LABELING	
20-Mar-2009	OTH OTHER/MISC./UNKNOWN	
23-Mar-2009	OTH OTHER/MISC./UNKNOWN	
23-Mar-2009	LB LABELING	
23-Mar-2009	OTH OTHER/MISC./UNKNOWN	
24-Mar-2009	LB LABELING	
25-Mar-2009	LB LABELING	
25-Mar-2009	OTH OTHER/MISC./UNKNOWN	
26-Mar-2009	LB LABELING	
26-Mar-2009	OTH OTHER/MISC./UNKNOWN	
30-Mar-2009	LB LABELING	
30-Mar-2009	LB LABELING	
03-Apr-2009	LB LABELING	
06-Apr-2009	LB LABELING	
07-Apr-2009	LB LABELING	
16-Apr-2009	LB LABELING	
17-Apr-2009	LB LABELING	

17-Apr-2009	OTH OTHER/MISC./UNKNOWN	
19-Apr-2009	OTH OTHER/MISC./UNKNOWN	
20-Apr-2009	LB LABELING	
20-Apr-2009	OTH OTHER/MISC./UNKNOWN	
24-Apr-2009	RFM REQUEST FOR MTG	
29-Apr-2009	OTH OTHER/MISC./UNKNOWN	
01-May-2009	RFM REQUEST FOR MTG	
04-May-2009	LB LABELING	
15-May-2009	LB LABELING	
15-May-2009	OTH OTHER/MISC./UNKNOWN	
18-May-2009	LB LABELING	
19-May-2009	MOM MINUTES OF MEETING	
21-May-2009	OTH OTHER/MISC./UNKNOWN	
04-Jun-2009	OTH OTHER/MISC./UNKNOWN	
10-Jun-2009	OTH OTHER/MISC./UNKNOWN	
25-Jun-2009	OTH OTHER/MISC./UNKNOWN	
26-Jun-2009	MOM MINUTES OF MEETING	
01-Jul-2009	APL APPROVAL LETTER	